UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs/Counterclaim-Defendants, v. TORRENT PHARMACEUTICALS LTD. and TORRENT PHARMA INC., Defendants/Counterclaim-Plaintiffs.	Civil Action No. 17-3186 (SRC)(CLW) (CONSOLIDATED)
TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs/Counterclaim-Defendants, v. INDOCO REMEDIES LTD., Defendant/Counterclaim-Plaintiffs.	Civil Action No. 17-7301 (SRC)(CLW)

JOINT FINAL PRETRIAL ORDER

JOINT PRETRIAL ORDER INDEX

This matter, having come before the Court for a final pretrial conference pursuant to Federal Rule of Civil Procedure 16; Saul Ewing Arnstein & Lehr LLP and Jones Day having appeared for plaintiffs Takeda Pharmaceutical Co. Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Limited ("Plaintiffs" or "Takeda"); Lerner David Littenberg Krumholz & Mentlik LLP and Pillsbury Winthrop Shaw Pittman LLP having appeared for defendants Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc. ("Torrent); and Klehr Harrison Harvey Branzburg LLP and Seyfarth Shaw LLP having appeared for defendant Indoco Remedies Ltd. ("Indoco," defendants Torrent and Indoco are collectively referred to herein as "Defendants"); and counsel all having been notified that:

(1) a nonjury trial in this matter has been scheduled before the Honorable Stanley R. Chesler on November 4, 2019; and

(2) a pretrial conference is scheduled before the Honorable Cathy L. Waldor on October 2, 2019 at 11:00 am EST at the United States District of New Jersey Martin Luther King Building & Courthouse, 50 Walnut Street Room 4D, Newark, NJ 07101.

The following Final Pretrial Order is hereby entered:

TAB 1

1. JURISDICTION

Takeda's actions against Torrent and Indoco in the United States District Court for the District of New Jersey (which were consolidated on May 16, 2019 by Judge Waldor) are patent infringement actions arising under the patent laws of the United States, including, but not limited to, 35 U.S.C. § 271 *et seq.* and 21 U.S.C. § 355, as amended by, *inter alia*, Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"), Pub. L. 98-417, § 101-106 & 202, 98 Stat. 1585 (1984), and Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. 108-173, §1 101-1108, 117 Stat. 2066, 2448-2464 (2003). This Court has subject matter jurisdiction over the consolidated action pursuant to the patent laws of the United States and 28 U.S.C. § 1331, 1338, 2201 and 2202. Plaintiffs and Defendants do not contest subject matter jurisdiction for the purposes of this consolidated action. Venue is proper in this District under 28 U.S.C. § 1391 and 1400(b). Plaintiffs and Defendants do not contest venue for purposes of this action.

TAB 2

2. PENDING/ CONTEMPLATED MOTIONS (Set forth all pending or contemplated motions, whether dispositive or addressed to discovery or the calendar. Also set forth the nature of the motion and the return date. If the court indicated that it would rule on any matter at pretrial, summarize that matter and each party's position).

A. Plaintiffs list the following motions:

a. Pending Motions:

None

b. Contemplated Motions:

None

B. Defendants list the following motions:

a. Pending Motions:

None

b. Contemplated Motions:

None

Plaintiffs and Defendants reserve the right to raise issues and seek pretrial rulings and/or a hearing on issues that relate to any matters included in the pretrial order that the parties have either not addressed or are unable to resolve prior to the submission of the pretrial order to the Court on September 25, 2019.

TAB 3

3. STIPULATION OF FACTS (Set forth in narrative form a comprehensive listing of all uncontested facts, including all answers to interrogatories and admissions, to which there is agreement among the parties).

The Parties submit these stipulated facts based on the status of the claims and defenses currently asserted in the action and reserve their right to modify, supplement, or amend these facts. The organization of the facts is exemplary, and the Parties reserve the right to reference the facts in their entirety for any issue in the case. These stipulated facts require no proof at trial and will become part of the evidentiary record in the action.

STIPULATION OF FACTS

The Parties

1. Plaintiff Takeda Pharmaceutical Company Ltd. is a Japanese corporation, having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan ("Takeda Japan").

2. Plaintiff Takeda Japan is the owner of record and assignee of U.S. Patent No. 7,807,689 ("the '689 patent") and has been at all times relevant to the case.

3. Plaintiff Takeda Pharmaceuticals U.S.A., Inc. is a Delaware corporation, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015 ("Takeda U.S.A.").

4. Plaintiff Takeda Pharmaceuticals America, Inc. is a Delaware corporation "(Takeda America"). It is a wholly owned subsidiary of Takeda U.S.A., having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015.

5. Plaintiff Takeda America has the right to sell Nesina®, Oseni®, and Kazano® in the United States.

6. Plaintiff Takeda Ireland Limited is a company incorporated under the laws of Ireland ("Takeda Ireland"). It is a wholly owned subsidiary of Takeda Japan and maintains its registered office at Bray Business Park, Kilruddery, Co. Wicklow, Ireland.

7. Plaintiff Takeda Ireland is the exclusive licensee of the '689 patent.

8. Defendant Torrent Pharmaceuticals Ltd. ("Torrent Ltd.") is a corporation organized and existing under the laws of India, having a registered and corporate office at Torrent House, Off Ashram Road, Ahmedabad, 380 009, Gujarat, India.

9. Defendant Torrent Pharma Inc. ("Torrent Pharma") is a corporation organized and existing under the laws of Delaware, having a place of business at 150 Allen Road, Suite 102, Basking Ridge, New Jersey 07920.

10. Defendant Indoco Remedies Ltd. ("Indoco") is a corporation organized under the laws of India having its principal place of business at Indoco House, 166 CST Road, Kalina, Santacruz (East), Mumbai 400098, India.

The Litigations and Withdrawal of Claims and Patents

11. Plaintiffs filed suit against Torrent for patent infringement on May 5, 2017 arising from Torrent's filing of Abbreviated New Drug Application ("ANDA") Nos. 21-0159, 21-0160, and 21-0161 with the United States Food and Drug Administration ("FDA") for

seeking approval to commercially manufacture and market generic version of Nesina®, Kazano®, and Oseni® ("Torrent's ANDA Products") prior to the expiration of the '689 patent.

12. On June 5, 2019 Plaintiffs and Torrent stipulated that Torrent's submission of its ANDA Nos. 21-0159, 21-0160, and 21-0161 to the FDA and its commercial manufacture, use, offer for sale, sale, or importation of Torrent's ANDA Products prior to the expiration of the '689 patent and certain claims therein would constitute literal infringement under 35 U.S.C. § 271 (a), (b), (c), or e(2)(A), if such claims were held valid and enforceable. (ECF No. 81). As a result of the stipulation, the only issue in dispute between Plaintiffs and Torrent was whether claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent were invalid.

13. Plaintiffs filed suit against Indoco for patent infringement on September 20, 2017 and January 3, 2018 arising from Indoco's filing of ANDA Nos. 210002 and 209998 with the FDA for seeking approval to commercially manufacture and market generic version of Nesina® and Kazano® ("Indoco's ANDA Products") prior to the expiration of the '689 patent.

14. On May 7, 2019 Plaintiffs and Indoco stipulated that Indoco's submission of its ANDA Nos. 209998 and 210002 to the FDA and its commercial manufacture, use, offer for sale, sale, or importation of Indoco's ANDA Products prior to the expiration of the '689 patent and certain claims therein would constitute infringement under 35 U.S.C. § 271 (a), (b), (c), or e(2)(A), if such claims were held valid and enforceable. (Case No. 2:17-cv-07301 ECF No. 56). As a result of the stipulation, the only issue in dispute between Plaintiffs and Torrent was whether claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent were invalid.

15. The Torrent and Indoco cases were consolidated for purposes of expert discovery and trial on May 16, 2019.

16. For purposes of trial, Takeda has agreed that it intends to assert only two claims of the '689 patent -- claims 4 and 12 —against Defendants. Thus, claims 4 and 12 of the '689 patent are the only claims remaining for trial.

The Patent-in-Suit

17. The '689 patent, entitled "Dipeptidyl Peptidase Inhibitors," was issued by the United States Patent and Trademark Office ("USPTO") on October 5, 2010.

18. The application immediately leading to the issuance of the '689 patent was filed on March 15, 2005 and claims priority to United States Provisional Patent Application No. 60/553,571, filed March 15, 2004, and United States Provisional Patent Application No. 60/629,524, filed on November 18, 2004.

19. Takeda obtained a patent extension under 35 U.S.C. § 154(b), which extended the term of the '689 patent by 1200 days.

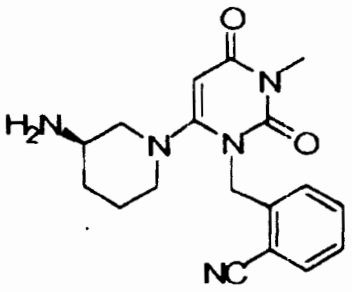
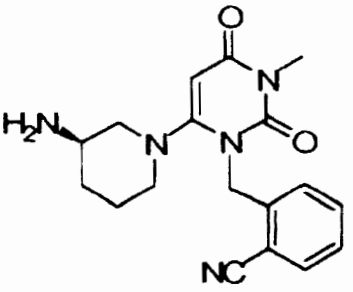
20. According to the Federal Drug Administration's ("FDA") Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), the '689 patent is listed as covering Takeda USA's Nesina®, Oseni®, and Kazano® products expiring on June 27, 2028.

21. On its face, the '689 patent lists Zhiyuan Zhang, Bruce J. Elder, Paul K. Isbester, Grant J. Palmer, and Luckner G. Ulysse as named inventors.

The Asserted Claims of the '689 Patent

22. As stated above, Plaintiffs assert that Torrent and Indoco's ANDA Products infringe claims 4 and 12 of the '689 patent, which cover the structure of the compound Alogliptin or pharmaceutically acceptable salts thereof, and the benzoate salt form of Alogliptin, respectively.

23. The structures of claims 4 and 12 of the '689 patent were corrected by a Certificate of Correction dated March 20, 2012 and are reproduced below in table form.

Claim 4 of the '689 Patent	**Claim 12 of the '689 Patent**
A compound of the formula  or pharmaceutically acceptable salts thereof	A compound of the formula  wherein the compound is present as a benzoate salt.

Takeda's NDAs for Nesina®, Kazano®, and Oseni®

24. Plaintiff Takeda U.S.A. is the registered holder of approved New Drug Application ("NDA") Nos. 22-271 (Nesina®), 22-426 (Oseni®), and 203-414 (Kazano®) indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

25. Specifically, Takeda U.S.A. holds approved NDA No. 22-271 for oral tablets containing 6.25 mg, 12.5 mg, and 25 mg of alogliptin benzoate, sold under the trade name Nesina®.

26. Specifically, Takeda U.S.A. holds approved NDA No. 22-426 for oral tablets containing alogliptin benzoate (12.5 mg/ 25 mg) and pioglitazone hydrochloride (15 mg/ 30 mg/ 45 mg), sold under the trade name Oseni®.

27. Specifically, Takeda U.S.A. holds approved NDA No. 203-414 for oral tablets containing alogliptin benzoate (12.5 mg) and metformin hydrochloride (500 mg/ 1000 mg), sold under the trade name Kazano®.

28. The FDA approved NDA Nos. 22-271 (Nesina®), 22-426 (Oseni®), and 203-414 (Kazano®) in 2013.

29. As discussed above, and pursuant to 21 U.S.C. § 355(b)(1), the '689 patent is listed in the FDA's Electronic Orange Book for each of Takeda U.S.A.'s marketed Nesina®, Oseni®, and Kazano® products.

30. Alogliptin is the only active ingredient in Nesina ®, while Kazano® and Oseni ® are combination products that include both Alogliptin and a second active ingredient (metformin and pioglitazone, respectively).

Defendants' ANDAs

31. Torrent Ltd. submitted to the FDA ANDA No. 21-0159 pursuant to 21 U.S.C. § 335(j), seeking approval to commercially manufacture, use, and market a generic version of the pharmaceutical drug product Nesina® in the form of oral tablets containing 6.25 mg, 12.5 mg, and 25 mg of alogliptin benzoate ("Torrent's Alogliptin ANDA Product"), prior to the expiration of the '689 patent. Torrent's ANDA No. 21-0159 relied upon the reference listed Nesina® NDA.

32. Takeda USA and Takeda Japan received a letter from Torrent Pharma on behalf of Torrent Ltd., dated April 3, 2017, with attached memoranda, stating that Torrent included certifications in its FDA submission, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that, *inter alia*, the '689 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Torrent's Alogliptin ANDA Product.

33. Torrent Ltd. submitted to the FDA ANDA No. 21-0160 pursuant to 21 U.S.C. § 335(j), seeking approval to commercially manufacture, use, and market a generic version of the pharmaceutical drug product Kazano® in the form of oral tablets containing 12.5 mg of alogliptin benzoate and 500 mg/1000 mg of metformin hydrochloride ("Torrent's Alogliptin-Metformin ANDA Product"), prior to the expiration of the '689 patent. Torrent's ANDA No. 21-0160 relied upon the reference listed Kazano® NDA.

34. Takeda USA and Takeda Japan received a letter from Torrent Pharma on behalf of Torrent Ltd., dated March 29, 2017, with attached memoranda, stating that Torrent included certifications in its FDA submission, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that, *inter alia*, the '689 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Torrent's Alogliptin-Metformin ANDA Product.

35. Torrent Ltd. submitted to the FDA ANDA No. 21-0161 pursuant to 21 U.S.C. § 335(j), seeking approval to commercially manufacture, use, and market a generic version of the pharmaceutical drug product Oseni® in the form of oral tablets containing 12.5 mg/25 mg of alogliptin benzoate and 15 mg/30 mg/45 mg of pioglitazone ("Torrent's Alogliptin Pioglitazone ANDA Product"), prior to the expiration of the '689 patent. Torrent's ANDA No. 21-0161 relied upon the reference listed Oseni® NDA.

36. Takeda USA and Takeda Japan received a letter from Torrent Pharma on behalf of Torrent Ltd., dated March 24, 2017, with attached memoranda, stating that Torrent included certifications in its FDA submission, pursuant to 21 U.S.C.§ 355(j)(2)(A)(vii)(IV), that, *inter alia*, the '689 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Torrent's Alogliptin Pioglitazone ANDA Product.

37. Indoco submitted to the FDA ANDA No. 210002 pursuant to 21 U.S.C. § 335(j), seeking approval to commercially manufacture, use, and market a generic version of the pharmaceutical drug product Nesina® in the form of oral tablets containing 6.25 mg, 12.5 mg, and 25 mg of alogliptin benzoate ("Indoco's Alogliptin ANDA Product"), prior to the expiration of the '689 patent. Indoco's ANDA No. 210002 relied upon the reference listed Nesina® NDA.

38. Takeda USA and Takeda Japan received a letter from Indoco, dated August 10, 2017, with an attached memorandum, stating that Indoco included a certification in its FDA submission, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that, *inter alia*, the '689 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Indoco's Alogliptin ANDA Product.

39. Indoco submitted to the FDA ANDA No. 209998 pursuant to 21 U.S.C. § 335(j), seeking approval to commercially manufacture, use, and market generic versions of the pharmaceutical drug product Kazano® in the form of oral tablets containing 12.5 mg/500 mg, and 12.5 mg/1 g of alogliptin benzoate and metformin hydrochloride ("Indoco's Alogliptin-Metformin ANDA Product"), prior to the expiration of the '689 patent. Indoco's ANDA No. 209998 relied upon the reference listed Kazano® NDA.

40. Takeda USA and Takeda Japan received a letter from Indoco, dated December 1, 2017, with an attached memorandum, stating that Indoco included a certification in its FDA submission, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that, *inter alia*, the '689 patent

is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Indoco's Alogliptin-Metformin ANDA Product.

Infringement

41. Defendants have stipulated that the commercial manufacture, use, offer for sale, sale or importation of products covered by their respective ANDA submissions prior to the expiration of the '689 patent will constitute infringement of claims 4 and 12 of the '689 patent under 35 U.S.C. § 271(a), (b), (c) or (e)(2)(A) if such claims are held valid and enforceable. Therefore, the only issue in dispute in the consolidated action is whether claims 4 and 12 of the '689 patent are valid.

Invalidity

42. Defendants contend that the '689 patent is invalid as obvious under the doctrine of obviousness-type double patenting and/or 35 U.S.C. § 103.

43. Defendants' theory based on obviousness-type double patenting is set forth in the reports of their expert Dr. David Rotella, dated June 14, 2019 and August 23, 2019.

44. Defendants' theory based on 35 U.S.C. § 103 is set forth in the reports of their expert Dr. Dana Ferraris, dated June 14, 2019 and August 23, 2019.

45. Plaintiff's expert, Dr. David Nichols submitted a rebuttal expert report on July 19, 2019, responding to the opening reports of Drs. Rotella and Ferraris.

TAB 4

4. JUDICIAL NOTICE—PLAINTIFFS

A. Plaintiffs requests that the Court take judicial notice of the following facts:

None.

B. Defendants object to the taking of judicial notice for the following reasons:

None. Defendants reserve the right to object to motions to take judicial notice if Plaintiffs make such motions.

TAB 5

5. JUDICIAL NOTICE—DEFENDANTS

A. Defendants request that the Court take judicial notice of the following facts:

None.

B. Plaintiffs object to the taking of judicial notice for the following reasons:

None. Plaintiffs reserve the right to object to motions to take judicial notice if Defendants make such motions.

TAB 6

6. PLAINTIFFS' CONTESTED FACTS (Stated separately for each defendant. Proof shall be limited at trial to the matters set forth below. Failure to set forth any matter shall be deemed a waiver thereof.)

A. Plaintiffs intend to prove the following contested facts with regard to liability:

In an effort not to overburden the Court with a voluminous submission of Contested Facts at this pre-trial stage, Plaintiffs have attempted to streamline their Contested Facts. Plaintiffs reserve the right to expound upon and/or provide additional detail, as necessary, to further support Plaintiffs' positions at trial, as well as Plaintiffs' pretrial brief. Plaintiffs incorporate by reference their expert's reports and the documents cited therein in full.

Finally, and for the avoidance of any doubt, Plaintiffs dispute and reserve all rights to introduce evidence and argument rebutting the statements set forth in Defendants' statement of Contested Facts (Tab 7) and statement of Legal Issues discussed *infra*, (Tab 19).

PLAINTIFFS' CONTESTED FACTS

Because Defendants have stipulated that their proposed generic Alogliptin products meet every limitation of claims 4 and 12 of the '689 patent, liability for infringement is conceded and will not require proof at trial. The only issue for trial is Defendants' claim that the '689 patent is invalid as obvious under 35 U.S.C. § 103 and/or the judicially-created doctrine of obviousness double patenting. On these issues, Defendants bear the burden of proof by clear and convincing evidence. Because Defendants bear the burden of overcoming the statutory presumption of validity to which the '689 patent is entitled, the presentation of facts for trial is their responsibility in the first instance, and Plaintiffs will respond. Plaintiffs have set forth below facts around the issues that they understand are in dispute. By listing these facts, Plaintiffs do not concede that Defendants have raised any genuine issues of material fact sufficient to warrant a trial on their invalidity defenses.

I. PERSON OF ORDINARY SKILL

1. A POSA would most likely have an advanced degree in chemistry or medicinal chemistry and at least one or two years of research experience in drug discovery. In some cases, the skilled person might have only a B.S. in organic or medicinal chemistry, but in that event would have five to ten years of experience in a drug discovery program.

2. The POSA that Defendants' experts apply and rely upon is a person having higher skills and more knowledge than a POSA, at least as of March 2004. For example, as of that time, non-peptidic-like substrate/inhibitor DPP-IV enzyme crystal structures were not available from which to apply an informed structure-based drug design technique in designing new non-peptidic-like DPP-IV inhibitors. A POSA would not be able to extract key structure-based information from peptidic-like substrate/inhibitor DPP-IV enzyme crystal structures, extrapolate the recognition and interactions identified between the DPP-IV enzyme active site and the

peptidic-like substrate/inhibitor, and then apply that information to the designing of non-peptidic DPP-IV inhibitors.

II. PRIORITY DATE OF THE '689 PATENT

3. The subject matter of the claims was invented no later than March 15, 2004, the date of the filing of provisional application No. 60/553,571 (the "'571 provisional") .

4. "Compound 4," as disclosed as an example of DPP-IV inhibitors on page 81 of the '571 provisional, is the compound known as Alogliptin as claimed in claim 4 of the '689 patent.

5. The '571 provisional further discloses the method of preparing Compound 4.

6. The '571 provisional further discloses that its compounds may be in the form of a pharmaceutically acceptable salt and includes benzoate in a list of acceptable salts.

III. NO COMBINATION OF REFERENCES RENDERS THE ASSERTED CLAIMS OBVIOUS

7. The FDA recognized Alogliptin as a new chemical entity that had not been used in any FDA-approved drug before.

8. Defendants have not identified any prior art reference that anticipates Alogliptin either explicitly or inherently

9. Defendants' expert, Dana Ferraris, Ph.D., argues that claim 4 of the '689 patent is obvious pursuant to 35 U.S.C. § 103 over:

(i) WO 2002/068420 A1 and its English-language equivalent CA 2,435,730 (the "**CA '730 patent**") or WO 2003/004496 (the "**WO '496 publication**") in view of:

(ii) the knowledge of one of ordinary skill in the art as of March 2004,

(iii) certain references that describe the known structural features of DPP-IV inhibitors, Dr. Ferraris labeled collectively as the "**Structure References**":

(a) Evans, D., "Dipeptidyl peptidase IV inhibitors," 5(6) IDrugs 577-585 (June 2002) ("**Evans**"),

(b) Wiedeman, P., et al., "Dipeptidyl Peptidase IV Inhibitors For The

Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes," 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003) ("**Wiedeman**"),

(c) Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV," 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003) ("**Lambeir**"),

(d) Engel, M., et al., "The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism," 100(9) PNAS 5063-068 (Apr. 29, 2003) ("**Engel**"), and/or

(e) Aertgeerts, K., et al., "Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation," 13(2) Protein Sci. 412-421 (Feb. 2004) ("**Aertgeerts**"), and/or

(iv) references that support substituting a uracil scaffold for a xanthine scaffold, Dr. Ferraris labeled collectively as the "**Substitution References**":

(a) U.S. Patent No. 5,142,051, "N Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity," issued Aug. 25, 1992 (the "**'051 patent**"),

(b) U.S. Patent No. 5,780,476, "Hydroxyl-Containing Xanthine Compounds," issued July 14, 1998 (the "**'476 patent**"), and/or

(c) Davies, T.G., et al., "Structure-based design of cyclin-dependent kinase inhibitors," 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002) ("**Davies**"), and/or

(v) references that disclose the benefits of single stereoisomers in pharmaceutical drugs as well as the use of mixed enantiomer compounds, Dr. Ferraris labeled collectively as the "**Stereoisomer References**":

(a) Campbell. D.B., Stereoselectivity in Clinical Pharmacokinetics and Drug Development, 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990) ("**Campbell**"),

(b) Hutt, A.J., The Development of Single-Isomer Molecules: Why and How, 7(4 supp. 1) CNS Spect. 14-22 (2002) ("**Hutt**"),

(c) Crossley, R., Chirality and the Biological Activity of Drugs, CRC Press (1995) ("**Crossley**"), and/or

(d) Izumi, T., et al., "*Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data*," 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997) ("**Izumi**").

10. Dr. Ferraris further argues that claim 12 of the '689 patent is obvious pursuant to 35 U.S.C. § 103 over the references cited above and further in view of one or more of these additional references:

> (vi) References regarding pharmaceutically acceptable salts, and how to efficiently develop and analyze pharmaceutical salts, Dr. Ferraris labeled collectively as the "**Salt References**":
>
> (a) Berge, S.M., et al., Pharmaceutical Salts, 66(1) J. Pharm. Sci., 1-19 (Jan. 1977) ("**Berge**"), and/or
>
> (b) Higgins, J.D. & Rocco, W.L., Pharmaceutical Preformulation, Today's Chemist at Work 22-26 (July 2003) ("**Higgins**").

11. Dr. Ferraris' two primary references – the CA '730 patent (via its WO equivalent (WO 2002/068420 A1)) and the WO '496 publication – were cited on the face of the '689 patent.

12. Dr. Ferraris' two primary references are presumed to have been considered by the examiner when determining the patentability of the '689 patent.

13. The Patent Office found the '689 patent claims patentable over the disclosures of the CA '730 patent and the WO '496 publication.

14. None of the cited prior art discloses all of the elements of the asserted claims of the '689 patent.

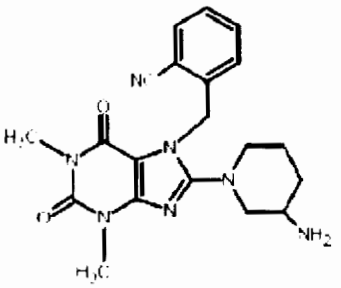
15. None of the cited prior art discloses the compound Alogliptin.

Choice of Lead Compound

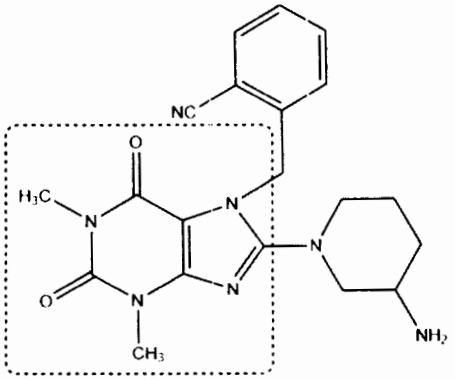
16. Alogliptin is a new chemical compound, and a *prima facie* case of obviousness for new compounds first requires that a defendant establish that a POSA would select and identify one or more lead compounds from the prior art for further development efforts.

17. Dr. Ferraris chooses only one proposed lead compound for his analysis, 1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine ("DCAX").

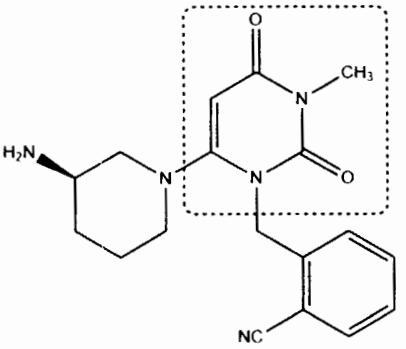
18. DCAX's chemical structure is below:



19. DCAX's chemical structure differs in several ways from Alogliptin.



DCAX



Alogliptin

20. The central ring system (also known as the "core" or "scaffold" (in dashed box, upper left)) of the DCAX compound is a derivative of a purine compound known as a xanthine (a double ringed structure in which a five-membered ring is fused to a six-membered ring).

21. The central ring of the Alogliptin compound (in dashed box, upper right) is a pyrimidine-dione (a single six-membered ring).

22. The central rings of the two compounds have different properties.

23. The xanthine core of DCAX is more water soluble and has a larger polar surface area relative to the pyrimidine-dione core of Alogliptin.

24. DCAX has four substituents attached to the central xanthine ring system, whereas Alogliptin has three substituents attached the central pyrimidine-dione ring system.

25. DCAX contains a guanidine moiety (combination of the ring-carbon attaching the ring-nitrogen of the piperidinyl ring and the two ring nitrogens within the five-membered ring of the xanthine ring system), whereas Alogliptin contains an amidine moiety (combination of the ring-carbon attaching ring-nitrogen of the piperidinyl ring and the one ring nitrogen of the pyrimidine-dione ring system).

26. The 3-amino-piperidinyl group of DCAX has unspecified stereochemistry, whereas Alogliptin is a single enantiomer.

27. The ring nitrogens in the six-membered ring of the central xanthine ring system in DCAX are in different positions from that of Alogliptin.

28. The 2-cyanobenzyl group and the 3-amino-piperdinyl group of DCAX occupy a different 3D-space relative to the carbonyls on the xanthine ring of DCAX, as compared to Alogliptin (i.e., the distances from these two groups to either of the carbonyls on the six-membered ring of the xanthine ring system of DCAX are greater than the distances from these two groups to either of the carbonyls on the central pyrimidine-dione ring system of Alogliptin).

29. To choose DCAX as a lead compound, a POSA would first have to consider Dr. Ferraris' selected references over numerous prior art references relating to DPP-IV inhibition.

30. The WO '496 publication offers no biological data at all for its disclosed compounds.

31. The CA '730 patent reports only in vitro tests of enzyme inhibition for about 10% of the prepared compounds, not in vivo efficacy testing.

32. The CA '730 patent provides no data on effects such as lipophilicity or solubility for any of the disclosed compounds.

33. The Wiedeman reference, which Defendants rely upon to support their invalidity arguments, is closer in time to the invention of the '689 patent than Dr. Ferraris' chosen primary references.

34. Dr. Wiedeman would at least be a POSA, if not more highly skilled in the art at the time of the invention.

35. The Wiedeman reference discusses many classes of DPP-IV inhibitors and specific compounds more potent than DCAX.

36. A POSA would next have to choose to focus on xanthine-based DPP-IV inhibitors over a diverse array of other known DPP-IV inhibitors.

37. The Wiedeman reference discloses that prior to the time of the invention, many peptidic molecules and "a number of non-peptidic molecules ha[d] been disclosed as DPP-IV inhibitors. These diverse groups of [non-peptidic] molecules include core structures such as xanthines, aminomethylisoquinolones, aminomethylisoquinolines, aminolactams and sulfonyltriazoles."

38. Dr. Ferraris offers no analysis of the peptidic compounds that were being studied prior to March 2004, nor why a POSA would not have looked to those molecules for a lead compound candidate. Yet Dr. Ferraris himself focused on peptidic compounds in his own work in the early 2000's attempting to develop a DPP-IV inhibitor.

39. Even as to non-peptidic compounds, several of these classes of molecules disclosed in the Wiedeman reference, including various pyrrolidine and cyanopyrrolidine-based DPP-IV inhibitors, had been studied more extensively than xanthines at the time of the invention, yet Dr. Ferraris does not discuss any compounds other than xanthines in his analysis.

40. The Wiedeman reference does not characterize compounds containing a xanthine core as the most promising DPP-IV inhibitors among the classes of non-peptidic DPP-IV inhibitors it discusses.

41. The Wiedeman reference discloses that "Eisai found carbamoyltriazoles to be potent inhibitors" at a stronger potency than any of the disclosed xanthine compounds.

42. Eisai's compound 32 (shown in Wiedeman's Figure 5), having a reported IC50 value of 347 pM, that is approximately twenty-eight times more potent than DCAX and is not xanthine-based.

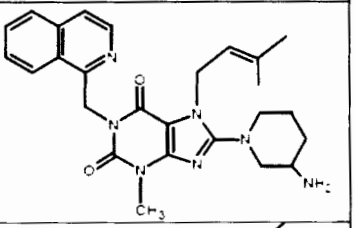
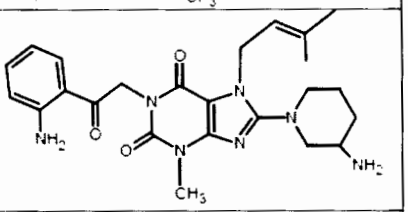
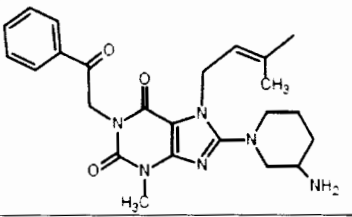
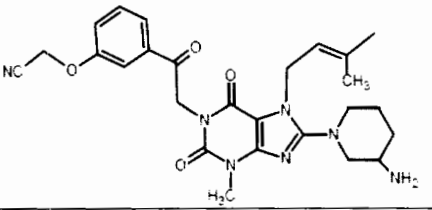
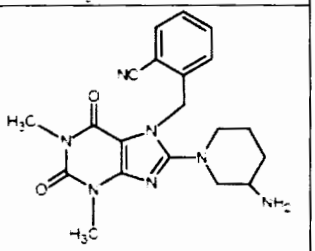
43. A POSA would then have to specifically choose DCAX as a lead compound over better-performing xanthine-based compounds disclosed in the same primary references.

44. Dr. Ferraris' primary references each disclose hundreds of other compounds that contain a xanthine core in addition to DCAX.

45. The CA '730 patent lists more than 800 xanthine-based compounds by name and generally describes other xanthine compounds, many of which showed greater potency than DCAX.

46. The CA '730 patent includes a table of 31 xanthine compounds – including DCAX (referred to in that table as "compound 1(121)") – as well as information on the biological activity of those compounds in inhibiting the DPP-IV enzyme.

47. Dr. Ferraris's report includes a table of five of these compounds, which includes DCAX:

IC_{50}	Compound	Structure
2 nM	**Compound 2(119):** 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 220:6-7)	
3 nM	**Compound 2(136):** 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-aminopiperidin-1-yl)-xanthine (CA '730 patent, Col. 223:14-15)	
5 nM	**Compound 2(28):** 1-(2-phenyl-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 204:24-25)	
6 nM	**Compound 2(88):** 1-[2-(3-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 214:26-27)	
10 nM	**Compound 1(121):** 1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine (CA '730 patent, Col. 197:13)	

48. Activity in the reference is described as an IC50 value (i.e., the amount of compound needed to produce 50% inhibition of an enzyme) against DPP-IV. The lower the IC_{50} value, the more active (more potent) the compound is in inhibiting DPP-IV, and vice versa.

49. Of the five highlighted compounds from the CA '730 patent, DCAX is the least active.

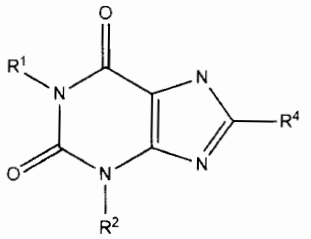
50. Dr. Ferraris states that a POSA "would not discount any of the 5 selected compounds because the difference in IC_{50} values … is neglible [*sic*, negligible]."

51. The CA '730 patent identifies Compound 2(119) and 2(28) as preferred.

52. From the CA '730 patent's results, Compound 2(119) is 5 times more potent in inhibiting the DPP-IV enzyme than DCAX (Compound 1(121)).

53. From the CA '730 patent's results, Compound 2(28) is 2 times more potent in inhibiting the DPP-IV enzyme than DCAX (Compound 1(121)).

54. Each of the four most-potent compounds reported in the CA '730 patent (referred to as compounds 2(119), 2(136), 2(28), and 2(88)) has a 3-methyl-2-buten-1-yl ("methyl butenyl") group at position seven of the fused bicyclic ring:



55. DCAX has a different moiety at that position, known as a "2-cyanobenzyl" group.

56. DCAX is the only compound of the 31 compounds with potency data in the CA '730 patent that includes a 2-cyanobenzyl group.

57. 25 of the 31 compounds with potency data include the methyl butenyl group.

58. Of the 38 compounds that the CA '730 patent identifies as "preferred compounds," 28 have the methyl butenyl group, and none include a 2-cyanobenzyl group like DCAX.

59. Of the 333 compounds prepared in the CA '730 patent, only 10 compounds included a 2-cyanobenzyl group (compounds 1(121), 1(137), 2(74), 2(75), 2(86), 2(92), 2(133), 2(145), 2(154), and 2(155)), whereas 255 compounds contained the methyl butenyl group.

60. The methyl butenyl group was contained in 25/31 compounds tested, in 255/333 compounds prepared, in 465/532 compounds further named, and in 28/38 of the preferred compounds listed in the CA '730 patent.

61. The second primary reference, the WO '496 publication, lists more than 100 xanthine-based compounds, including DCAX.

62. The WO '496 publication does not provide biological data for any of the disclosed xanthine-based compounds.

63. The WO '496 publication does not disclose what level of inhibition would be considered "potent" or what the inhibitors are "selective" over.

64. There is no information in the WO '496 patent that would instruct a POSA regarding the effectiveness of DCAX in inhibiting DPP-IV or its effectiveness in inhibiting DPP_IV in comparison to the other disclosed xanthine-based compounds.

65. DCAX is identified in both primary references identified by Dr. Ferraris.

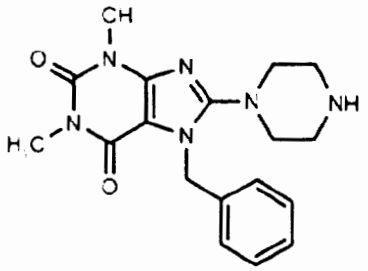
66. At least seven other compounds are also disclosed in both primary references.

67. Specifically, the CA '730 patent compounds of Examples 1, 1(2), 1(9), 1(10), 1(121), 1(124), 1(138), and 10(135) overlap with the WO '496 publication compounds of Examples 2-4 (racemate, S-isomer, and R-isomer), Example 17 (R-isomer), Example 103 (R-isomer), Example 44 (racemate), Example 1 (racemate), Example 46 (racemate), Example 9 (racemate), and Examples 10 (racemate) and 20 (R-isomer), respectively.

68. The Wiedeman reference states that the CA '730 patent discloses "a number of very potent inhibitors," and specifically cited a compound denoted as 2(136) –the second best performer of the four most active compounds.

69. Wiedeman also references the WO '496 patent.

70. The Wiedeman reference states that a compound from the same researchers that published the WO '496 patent was selected for evaluation in later studies and was considered "attractive":



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(Novo Nordisk)

71. The compound identified as "attractive" does not contain either the 3-aminopiperdinyl or 2-cyanobenzyl groups that comprise DCAX.

72. The Wiedeman reference does not discuss DCAX as a compound that was studied further or warranted study.

73. The Wiedeman reference does not comment on DCAX's disclosure in both the CA '730 patent and the WO '496 publication.

74. Dr. Ferraris states that the same research group associated with the CA '730 patent at Boehringer Ingelheim also disclosed additional DPP-IV inhibitory compounds in the CA 2,496,249 patent ("Mark 2004") that contain a xanthine core and some of which also include both the 2-cyanobenzyl and 3-aminopiperdinyl groups.

75. Dr. Ferraris states the disclosure of xanthine compounds 2(12) and 2(17) in Mark 2004, each containing a 2-cyanobenzyl group and a 3-aminopiperdinyl group, and which were reported as having DPP-IV inhibitory activity with IC50 values of 16 nM and 32 nM, respectively, would indicate to the POSA that the cyano group (as the 2-cyanobenzyl) and the 3-

aminopiperdinyl group were important structural elements that lead to increased inhibitory potency against DPP-IV.

76. None of the 30 compounds listed as particularly preferred compounds in Mark 2004 contain a 2-cyanobenzyl group, at the 7 position of the xanthine core.

77. Of the 46 compounds tested and reported with IC50 values in Mark 2004, none of the 6 compounds exhibiting the highest potency of 1 nM contain a 2-cyanobenzyl group, and none of the 34 compounds exhibiting a high potency with IC50 values ranging from 1 nM to 10 nM contain a 2-cyanobenzyl group at the 7-position of the xanthine core.

78. Only 3 compounds having a 2-cyanobenzyl group at the 7-position of the xanthine core were tested and reported with IC50 values in Mark 2004 — compounds 2(9), 2(12), and 2(17) — and these were the 45th, 41st, and 43rd least potent of the 46 compounds tested, respectively.

79. The most potent compounds reported in Mark 2004: 2(80), 2(99), 2(132), 2(142), 2(148), and 1(150), all exhibiting an IC50 of 1 nM — have the following groups at the 7-position: (2-butyn-1-yl), (2-butyn-1-yl), (2-butyn-1-yl), (2-butyn-1-yl), (2-buten-1-yl), and (2-buten-1-yl).

80. Nowhere does Mark 2004 teach preferring a 2-cyanobenzyl group at the 7-position.

81. The inventors of the '730 patent and Mark 2004 chose a different compound, not DCAX, for development into a DPP-IV inhibitor. That compound was included by the inventors in a list of "preferred" compounds (DCAX was not), and it had better biological activity than DCAX.

Pathway from DCAX to Alogliptin

82. To get from DCAX to Alogliptin, a POSA would have to first choose to replace the core bicyclic xanthine scaffold of DCAX with a new, monocyclic uracil scaffold.

83. Dr. Ferraris stated that a POSA would choose DCAX as a lead compound because of "the interest in non-peptidic DPP-IV inhibitors containing a xanthine core."

84. Dr. Ferraris suggests that a POSA would change the xanthine core because she (1) would want to reduce the molecular weight of a core scaffold; (2) "would have substituted one ring structure for a two ring structure in Compound 1(121) to see if the compound retained its potency and determine whether the two ring structure was essential" and (3) "would naturally consider replacing xanthine with other nitrogen-containing bases." He also suggests that the POSA would be motivated to change from a xanthine core because of "IP concerns," but does not identify any patents or applications that would have led the POSA to make such a change.

85. Dr. Ferraris suggests that a POSA would replace the xanthine core with a uracil core using a "scaffold hopping" process.

86. Dr. Ferraris relies on Böhm 2004 as support for his scaffold hopping theory.

87. Böhm 2004 is not prior art to the invention of the '689 patent.

88. Böhm 2004 states that "serendipity has played a large role in many of" its examples and notes "the challenges of the filed that are still unsolved."

89. Böhm 2004 further states:

> So, why is the usage and the number of successful applications not larger? One possible explanation is that for a new target, it takes time to understand the relative importance of the different pharmacophore features. Multiple binding modes can sometimes obscure the picture and the interpretation of the structure-activity relationships can be misleading without knowledge of the 3D structure of the target. Another possible contributor is the limited success of the peptidomimetic approach. Many pharmaceutical companies have invested heavily in the past in peptide chemistry

> and subsequent effort to convert biologically active peptides into metabolically stable non-peptidic molecules. A further limitation is that synthetic tractability has not been taken into account in many computational approaches.

90. There is no evidence that DCAX or its analogous compounds had been studied to determine which parts of the molecule demonstrated essential features to DPP-IV inhibition and which parts of the molecule were not necessary to DPP-IV inhibition.

91. There is no evidence that DCAX was actually in use on or before March 15, 2004 (or indeed at any time) as a lead compound.

92. A POSA as of March 15, 2004, had no structure-based DPP-IV crystallographic information indicating that a cyano group attached to a phenyl (e.g., a 2-cyanobenzyl group) in a non peptidic-type DPP-IV inhibitor behaved in any way like a cyano group attached to a pyrrolidine in a peptidic-type DPP-IV inhibitor.

93. Changing a single atom in a molecule may impact the steric, electronic, and hydrophobic character of a drug, affecting not only its ability to engage the biological target, but also its pharmacokinetic properties.

94. Changing the central core (scaffold) of a compound may involve more than changing a single atom.

95. A POSA may not be able to predict whether a new chemical compound will have particular pharmacological properties even when analogous compounds may be known.

96. Dr. Ferraris' primary references do not teach or suggest Dr. Ferraris' scaffold hopping theory.

97. Dr. Ferraris' "Structure References"—Evans, Wiedeman, Lambeir, Engel, and Aertgeerts—discuss various crystal structures of the DPP-IV enzyme bound with peptidic-like agents, but they do not disclose a crystal structure of the DPP-IV enzyme bound with a non-

peptidic like agent, much less a xanthine based DPP-IV inhibitor (such as DCAX) or a pyrimidine-dione based DPP-IV inhibitor (such as Alogliptin).

98. At the time of the invention, there were no known crystal structures of the DPP-IV enzyme bound with non-peptidic like agents to indicate that DCAX would bind and be oriented within the active site of the DPP-IV enzyme in a fashion similar to a peptidic-like compound.

99. The Structure References do not disclose what portion of a non-peptidic inhibitor would bind in the S1 pocket and/or the S2 pocket, how particular groups would be positioned in such pockets, or what specific DDP-IV enzyme interactions would be involved in the binding of the inhibitor.

100. Zhang 2011 is a reference from one of the inventors of the '689 patent that describes the process the inventors took to develop Alogliptin. Zhang is at least a POSA.

101. Feng 2007 is a reference from one of the inventors of the '689 patent, Zhang, that further describes the process the inventors took to develop Alogliptin.

102. Zhang 2011 and Feng 2007 disclose that the inventors did not immediately change the scaffold of their compound, but first changed substituents on their lead molecules to see if they could optimize them into effective treatments, and designed scaffold changes based on information from DPP-IV crystal structures bound with non-peptidic inhibitors bound.

103. Both of Dr. Ferraris' primary references focus on xanthine-based core structures and their DPP-IV inhibitive potential.

104. Dr. Ferraris' primary references do not disclose compounds with a monocyclic uracil scaffold.

105. Dr. Ferraris' primary references do not suggest that replacing the scaffold of the disclosed xanthine-based compounds would improve DPP-IV inhibition or result in any other improved features.

106. Dr. Ferraris' primary references do not suggest that uracil scaffolds would improve DPP-IV inhibition or result in any other improved features.

107. Dr. Ferraris does not identify any prior art references that teach or suggest specifically replacing a xanthine core with a uracil in developing a DPP-IV inhibitor.

108. The xanthine central ring system in compounds like DCAX have different properties from the uracil central ring system in Alogliptin, such as molecular weight, total surface area, melting point, water solubility, and pKa.

109. Dr. Ferraris suggests three references, referred to as "Substitution References" – the '051 patent, the '476 patent, and Davies – provide motivation for a POSA to change the xanthine core of DCAX to uracil.

110. The '051 patent, the '476 patent, and Davies do not discuss DPP-IV inhibition or suggest that their teachings could be used to develop improved DPP-IV inhibitors.

111. The '051 patent is directed to antiviral compounds.

112. The '476 patent is directed to the inhibition of intracellular signaling events unrelated to DPP-IV.

113. The Davies reference is directed to CDK enzyme inhibitors.

114. In each of those references, xanthine and uracil are two of multiple classes of chemical rings that could be used for targets.

115. None of the references disclose a preference for specifically replacing xanthine with uracil.

116. The prior art stated that using "6- or 7-membered rings," like that in Alogliptin, would "result[] in a loss of potency."

117. Next, a POSA would have to choose to retain some of DCAX's substituents while discarding other substituents.

118. There are potential safety and other risks inherent in changing substituents.

119. The 2-cyanobenzyl and 3-aminopiperidinyl groups that Dr. Ferraris argues would be retained from DCAX are located on the five-membered ring of the xanthine/purine bicyclic ring system. These groups are located on Alogliptin's six-membered monocyclic ring system.

120. Moving the 2-cyanobenzyl and 3-aminopiperidinyl groups from the five membered ring of xanthine to the six-membered monocyclic ring system would "shift" these groups relative to the 3D-arrangement of the remaining portions of the respective compounds.

121. Next, a POSA would have to choose a specific orientation of the selected groups about the new monocyclic uracil scaffold.

122. Replacing the central ring of DCAX with uracil would lead to four possible orientations.

123. Next, a POSA would have to choose to add a further substituent on the resulting new molecular framework so as include all the various structural components of Alogliptin.

124. Alogliptin does not have uracil as a base, but has *N*-methylated uracil.

125. Next, a POSA would have to choose a specific enantiomer of the amino group on the resulting new molecular framework to include the specific stereoisomer of Alogliptin.

126. Alogliptin is a single enantiomer in which the 3-amino group of the 3-aminopiperidinyl group has an (R)-configuration.

127. Nothing in Dr. Ferraris' primary references teaches or suggests the need for selecting a specified stereoisomer.

128. Dr. Ferraris suggests that a POSA would select between stereoisomers through "routine practice."

129. The CA '730 patent includes both stereoisomers of three separate compounds among the "preferred" list, indicating no particular preference between stereoisomers.

130. Dr. Ferraris cites to four references, referred to as "Stereoisomer References," which he suggests provide motivation to choose the specific stereoisomer in Alogliptin – Campbell, Hutt, Crossley, and Izumi.

131. None of these references disclose or suggest that compounds similar in structure to Alogliptin would exhibit more efficacy or improved properties if a POSA were to choose Alogliptin's specific stereoisomer.

132. Finally, with respect to claim 12 of the '689 patent, a POSA would have to choose a specific, yet rarely utilized, benzoate salt.

133. The WO '496 publication does not highlight a benzoic acid salt specifically, but rather includes it among an exemplary list of possible organic and mineral acids to form salts.

134. Of the 103 compounds prepared in the WO '496 publication, only HCl or TFA salts were prepared.

135. The choice of salt depends on many factors, including the desired bioavailability, solubility, formulation properties and cost.

136. Berge states "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound," and "selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice."

137. The Berge reference was published in 1977.

138. Since 1977, literature has stated that benzoate is "rarely [used] for salt formation."

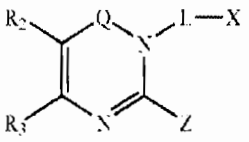
IV. THE ASSERTED CLAIMS ARE NOT OBVIOUS OVER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING

139. Defendants' other expert, David P. Rotella, Ph.D., argues that claims 4 and 12 of the '689 patent are obvious under the judicially-created doctrine of obviousness-type double patenting. Specifically, he argues that the claims are invalid over claim 162 (of 169 total claims) of U.S. Patent No. 7,723,344 (the "**'344 patent**") in view of Kim, et al., "Anti-diabetic Activity of Constituents of Lycii Fructus," The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("**Kim 1998**"), and further in view of common knowledge available to a POSA.

140. To establish obviousness-type double patenting, a party first must demonstrate that the asserted claims are not patentably distinct from one or more claims in a different, earlier-expiring patent.

141. The publication that resulted in the '344 patent was cited on the face of the '689 patent.

142. The '344 patent is directed to DPP-IV inhibitors. As shown in the Abstract (and below), the '344 patent is directed to compounds of Formula I, which are pyrimidine-based compounds:



I

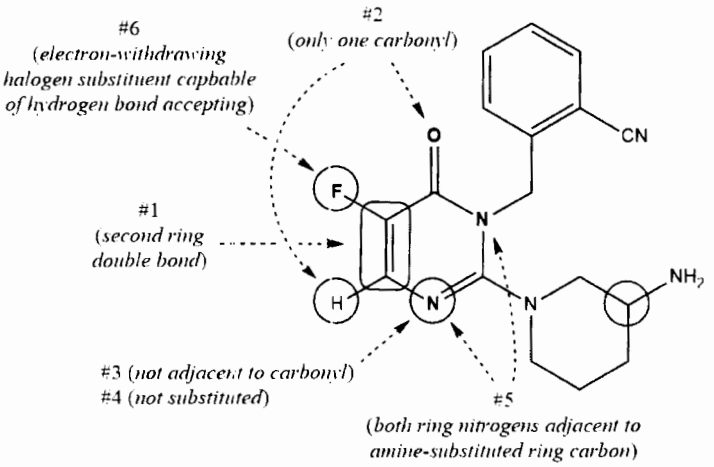
143. Each of the final compounds prepared in the '344 patent are multi-ring compounds where the central pyrimidine ring system is a pyrimidinone ring.

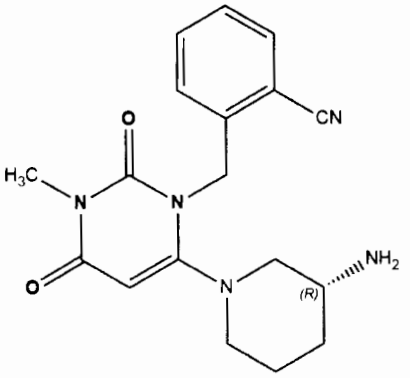
144. Each of the final compounds prepared in the '344 patent – including that claimed in claim 162 – has a central pyrimidinone ring system with (1) two double bonds; (2) at most one ring carbonyl; and (3) only one of the ring nitrogen atoms is adjacent to a ring carbonyl.

145. Dr. Rotella's starting point for his analysis is based solely upon the disclosure of the compound in one claim, claim 162 of the '344 patent.

146. Alogliptin is not disclosed or contemplated in the '344 patent.

147. The structure of the compound in claim 162 of the '344 patent and the structure of Alogliptin is depicted below (with annotations):





Claim 162 of the '344 patent **Alogliptin**

148. The compounds differ in that there are different configurations of the central ring nitrogen atoms (marked in blue) and carbon atoms, and there are different single and double bond arrangements (boxed in red).

149. The compounds further differ in that the compound of claim 162 includes a halogen substituent (fluorine, F, circled in red) and a hydrogen substituent (H, circled in red) adjacent to each other.

150. The compounds further differ in that Claim 162 does not specify a stereoisomer of the compound (circled in blue).

151. The following table includes differences between the central ring of the compound of claim 162 and Alogliptin:

	Central ring compound of claim 162	**Central ring Alogliptin**
(1)	two ring double bonds	one ring double bond
(2)	one carbonyl	two carbonyls
(3)	only one of two ring nitrogens adjacent to a carbonyl	both ring nitrogens adjacent to at least one carbonyl
(4)	one of two ring nitrogens substituted with a pendant group	both ring nitrogens substituted with pendant groups;
(5)	both ring nitrogens adjacent to the amine-substituted ring carbon	only one ring nitrogen adjacent to the amine-substituted ring carbon
(6)	ring *carbon* substituted with an electron-withdrawing substituent capable of forming hydrogen bonds as a hydrogen-bond acceptor (*i.e.*, a fluorine atom)	ring *nitrogen* substituted with a hydrophobic, and mildly electron-donating substituent that is unable to form hydrogen bonds (*i.e.*, a methyl group)

152. In the context of claim 12 of the '689 patent, claim 162 does not mention the benzoate salt, whereas claim 12 of the '689 patent requires that specific salt.

153. Every compound in the '344 patent exhibits differences (1) through (5) identified above.

154. Six of the 36 compounds exemplified in the '344 patent had difference (6) as well.

155. Compound of claim 162 is a potent DPP-IV inhibitor. The '344 patent did not report specific potency data against the DPP-IV enzyme for any of the prepared compounds, but stated "the apparent inhibition constants (K_i) for compounds, against DPP-IV, were in the range from about 10^{-9} M to about 10^{-5} M."

Dr. Rotella's Scaffold Replacement Theory of OTDP

156. Dr. Rotella argues that the change from claim 162 compound to Alogliptin would be a "simple" "two-step" scaffold replacement.

157. A POSA would have to replace the pyrimidinone central ring system of the compound of claim 162 with the pyrimidine-dione ring system of uracil via scaffold replacement— i.e., "scaffold hopping".

158. There is no evidence that any scaffold hopping method was being used in the study of DPP-IV inhibition at the time of the invention.

159. There is no reported evidence regarding claim 162 compound or its analogous compounds identifying which parts of the molecule were demonstrated as essential features to DPP-IV inhibition and which parts of the molecule were not necessary to DPP-IV inhibition.

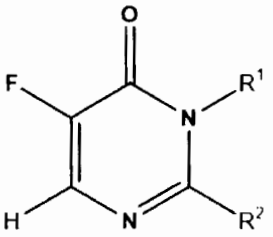
160. Dr. Rotella argues a POSA would create a model from co-crystal structures of DPP-IV enzyme with peptidic DPP-IV inhibitors that bind to its active site, screen databases of "all DPP-IV inhibitors and small molecules that were known to bind DPP-IV," and after iterative evaluations and further modifications of potential compounds, i.e., "computer-aided scaffold replacement and fragment-based screening," eventually identify a potent, selective DPP-IV inhibitor.

161. Changing a single atom in a molecule may impact the steric, electronic, and hydrophobic character of a drug, affecting not only its ability to engage the biological target, but also its pharmacokinetic properties.

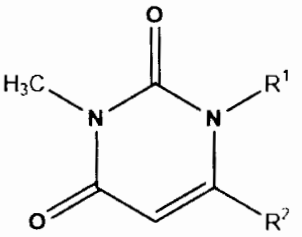
162. Changing the central core (scaffold) of a compound may involve more than changing a single atom.

163. The '344 patent or Kim 1998 does not teach or suggest scaffold hopping.

164. The central ring system of the compound of claim 162 is a pyrimidinone ring system (shown below, left), which is the same central ring system in each of the thirty six final compounds prepared in the '344 patent. (*See* the '344 patent at col. 120, lines 16-31 and col. 66, line 43 to col. 100, line 18, respectively). In contrast, the central ring system of Alogliptin is a pyrimidine-dione (shown below, right).



Pyrimidinone
(claim 162)
(and '344 patent generally)



pyrimidine-dione
(Alogliptin)

165. The '344 patent did not disclose the preparation of any pyrimidine-dione compounds, much less provide any data associated with a pyrimidine-dione compound.

166. The '344 patent does not disclose uracil cores.

167. Dr. Rotella argues that a POSA would have chosen to replace the pyrimidinone-based scaffold of the compound of claim 162 with uracil because the uracil compound itself was described in Kim 1998 as having anti-diabetic activity.

168. Kim 1998 does not mention type 2 diabetes or the DPP-IV enzyme. No POSA searching for references relating to development of DPP-IV inhibitors would have found or considered Kim 1998.

169. Kim 1998 does not mention whether uracil inhibits the DPP-IV enzyme or whether uracil's anti-diabetic activity is related to DPP-IV activity or is specific for type II diabetes.

170. Nothing in Kim 1998 suggests that uracil would have been particularly promising in treating diabetes among the compounds tested.

171. Kim 1998 reports that the compound "Rutin" had the highest total inhibition and Daonil® had the best inhibition-to-dose ratio. Uracil scored on par with ascorbic acid (Vitamin C) in terms of blood glucose inhibition rates (18.3% versus 18.1%).

172. The Wiedeman reference describes multiple classes of known DPP-IV enzyme inhibitors which may be useful in treating type II diabetes—and does not mention uracil among the DPP-IV inhibitors.

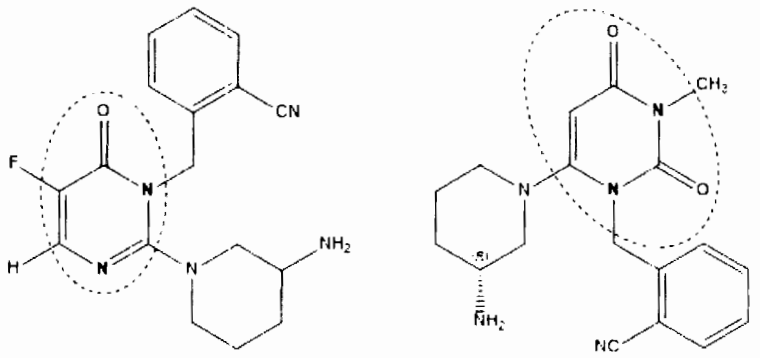
173. Other references at the time identified additional promising anti-diabetes compounds that had been tested in controlled clinical trials, unlike those in Kim 1998.

174. Next, a POSA would have to retain some substituents on the compound of claim 162 while discarding others.

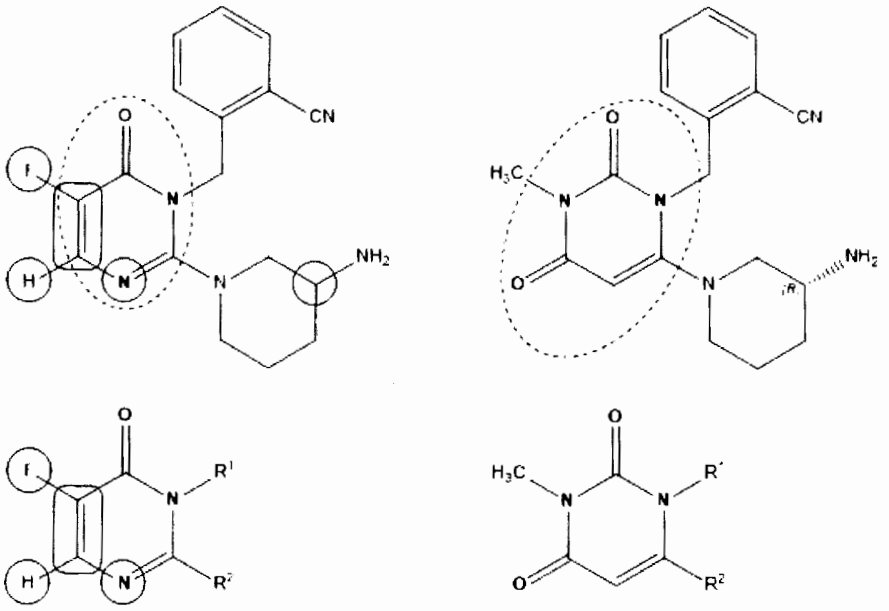
175. Dr. Rotella provides no indication what would motivate a POSA to make those specific changes.

176. Next, a POSA would have to choose a specific orientation (substitution pattern) of the selectively retained groups about the new uracil scaffold.

177. A pyrimidinone and uracil would be oriented differently in Dr. Rotella's proposed pathway:



178. Upon aligning Dr. Rotella's "retained" 2-cyanobenzyl and 3-aminopiperidinyl groups (two upper structures shown below), there would be multiple differences (two lower structures shown below, with Dr. Rotella's "retained" 2-cyanobenzyl and 3-aminopiperidinyl groups labelled as R^1 and R^2, respectively, for purposes of clarity).



179. The differences include rearranging the ring nitrogens, replacing a ring C-H group of claim 162 with a ring carbonyl of Alogliptin, and replacing a ring C-F group with a ring N-methyl group.

180. Dr. Rotella's proposed pathway would require a POSA to maintain the two retained groups in an adjacent relationship, to discard the fluorine substituent to avoid producing an N-fluoro group, and further to discard one of four possible structures ("compound (2)") as it contains a hydrazine moiety.

181. Dr. Rotella asserts there would be four possible options if one were to replace the central ring with uracil, and labels the resulting compounds 1-4.

182. Dr. Rotella argues that a POSA would have discarded compound (2) because it includes a hydrazine.

183. Many active pharmaceutical ingredients include hydrazines.

184. Dr. Rotella concedes that a POSA would "further optimiz[e]" three of the four possible compounds.

185. Next, a POSA would have to further modify the amide group as an N-methyl amide group.

186. Finally, a POSA would have to choose a specific enantiomer (the (*R*)-enantiomer configuration).

187. The compound of claim 4 has a single stereocenter located on the 3-aminopiperidinyl group attached to the pyrimidine-dione central ring system such that the compound of claim 4 has an (*R*)-enantiomer configuration.

188. In the context of claim 12 of the '689 patent, a POSA would further have to choose the benzoate salt.

Dr. Rotella's Fluoro-olefin Theory:

189. Dr. Rotella also proposes the fluoro-olefin theory in which he argues that, because a fluoro-olefin group has been used to replace an amide group in the past (replacing the carbonyl of the amide ("C=O") with a carbon-fluorine bond ("C-F") and replacing the nitrogen-hydrogen bond of the amide ("N-H") with a carbon-hydrogen bond ("C-H")), a POSA would also be motivated to do the reverse and replace a fluoro-olefin with an amide.

190. Dr. Rotella asserts that a POSA would be motivated to "directly replace the pyrimidinone scaffold in the compound of claim 162 of the ['344] patent with a pyrimidine[-]dione scaffold (uracil)" because it was "commonly known in the art that a fluoro-olefin mimics

an amide bond in DPP-IV inhibitors, i.e., replacement of the fluoro-olefin moiety with amide bond would result in an active DPP-IV inhibitor."

191. Every example cited by Dr. Rotella runs in only one direction – replacing an amide with a fluoro-olefin group, not the reverse.

192. The replacements Dr. Rotella refers to in the prior art were all made to address the biological instabilities observed in the amide containing compounds by providing a more stable fluoro-olefin group. Dr Rotella points to no observed issues with stability of the claim 162 compound.

193. The modification of a compound with a group like an amide can impact the "size, shape, electronic distribution, lipid solubility, water solubility, pKa, chemical reactivity, and hydrogen bonding."

194. Replacing a fluoro-olefin group with an amide group requires that the fluorine substituent of the fluoro-olefin be aligned with the oxygen substituent of the amide which it is replacing.

195. Specifically, as shown in the figure below, excerpted Figure 32 from Lee 1990, the fluorine atom of the fluoro-olefin and the oxygen of the amide group are aligned—not the C-F bond aligned with the N-H bond.

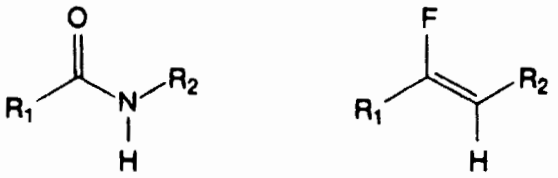
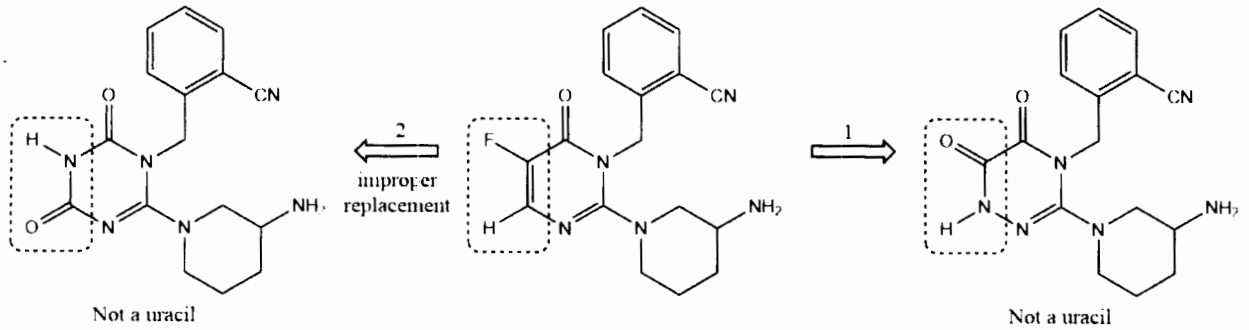


Fig. 32 Fluoroolefins as amide bond isosteres.

196. Every example cited by Dr. Rotella, replacing an amide with a fluoro-olefin group, has the alignment shown above, with the C-F bond of the fluoro-olefin replacing the carbonyl group of the amide group (i.e., the C-F bond does not replace the N-H bond of the amide).

197. Replacing the fluoro-olefin in the compound of claim 162, identified by the hashed box in the figure below, with an amide by either route does ***not*** result in a "uracil ring in the core structure" under either situation:



198. Dr. Rotella's fluoro-olefin theory misaligns the groups being replaced, requiring replacement of the C-F bond with an N-H (not a C=O) and a C-H with a C=O (not an N-H).

V. SECONDARY CONSIDERATIONS

199. Alogliptin's safety and efficacy were unexpected.

200. The DPP-4 inhibitors that existed before Alogliptin were not very selective for DPP-4 over other DPP enzymes. That was problematic because "[i]nhibition of DPP-8 and DPP-9 has been associated with toxicity in animals." (Feng 2007 at 2300 n.14 (*citing* Lankas, George R., et al., *Dipeptidyl Peptidase IV Inhibition for the Treatment of Type 2 Diabetes*, 54 DIABETES 2988 (2005).) The inventors of the '689 patent, however, discovered that Alogliptin "is a potent (IC_{50} < 10 nM) inhibitor of DPP-4 and exhibits greater than 10,000-fold selectivity over the closely related serine proteases DPP-8 and DPP-9," and this unexpected selectivity continues to be recognized. (Feng 2007 at 2300; Agarwal, Ritesh, et al., *Novel Serine Protease*

Dipeptidyl Peptidase IV Inhibitor: Alogliptin, 12 MINI-REVIEWS IN MED. CHEM. 1345, 1348 (2012); Bumsup, Lee, et al., *Pharmacokinetic, Pharmacodynamic, and Efficacy Profiles of Alogliptin, a Novel Inhibitor of Dipeptidyl Peptidase-4, in Rats, Dogs, and Monkeys*, 589 EUR. J. PHARMACOLOGY 306 (2008).)

201. There is nothing taught in any of the references cited by Defendants, or by experts Drs. Ferraris or Rotella, that suggests that Alogliptin has high specificity for DPP-4 over DPP-8 or DPP-9. The POSA would have no knowledge of the selectivity of Alogliptin.

202. The xanthine-based prior-art DPP-4 inhibitors have significant π-stacking capabilities because xanthine has two fused rings. The favorable interaction created by π-stacking would help stabilize the molecule.

203. A POSA would expect that replacing a bicyclic ring with a monocyclic ring would reduce the π-π interaction, because the Alogliptin now has a smaller π-bonding surface. Indeed, crystal structures show that to be true. (*Compare* Zhang 2011 at Figs. 1 & 2 (showing significant π-stacking between Y547, the tyrosine of DPP-4, and the xanthine rings), *with* Fig. 9 (showing less alignment between Y547 and the pyrimidine-dione ring of Alogliptin).)

204. A POSA would expect that the decreased interaction between Alogliptin and DPP-4 would reduce the stability, thus rendering Alogliptin a less potent inhibitor. Surprisingly, Alogliptin is a more potent DPP-4 inhibitor.

205. The choice of the benzoate salt specifically produced further unexpected results and required significant work. The inventors tested numerous salts for suitability, including tosylate, hydrochloride, and sulfate. The initial phase of salt screening involved about 200 crystallizations on each of three compounds, one of which was Alogliptin, which involved 15

counterions and 12 solvents. The inventors tested thermostability, water solubility, ease of crystallization, hygroscopicity, polymorphism, and whether hydrates were formed.

206. It was only after that extensive experimental process that the inventors concluded that the benzoate salt had the best overall properties to move forward in clinical development. The inventors subsequently identified the benzoate salt as the most desirable due to its enhanced thermal stability compared to the Alogliptin free base, its increased solubility under aqueous conditions, and the fact that it did not absorb moisture or form a hydrate.

207. The benzoate salt also lasted longer in the body. The rarely used benzoate salt's optimal properties for Alogliptin were unexpected.

208. The prior art taught away from Alogliptin. For example, Villhauer discloses that the simplest DPP-4 inhibitors are pyrrolidines, and "[s]ubstituting the pyrrolidine ring with 6- or 7-membered rings or acyclic amines results in a loss of potency." (ANNUAL REPORTS at 194.) Alogliptin contains two rings attached to a pyrimidine-dione core, both of which are 6-membered rings. A POSA would believe that such rings would result in loss of potency.

VI. REMEDIES

209. Plaintiffs are entitled to a judgment that Defendants have infringed claims 4 and 12 of the '689 patent.

210. Plaintiffs are entitled to a judgment ordering that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA Nos. 21-0159, 21-0160, 21-0161, 210002, and 209998 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be any earlier than June 27, 2028, the expiration date of the '689 patent.

VII. RESERVATION

211. The facts stated within are not exhaustive and are merely representative of the facts that Plaintiffs may present evidence of at trial. Plaintiffs reserve the right to present these

and any such additional facts that are commensurate with their interrogatory responses, deposition testimony, expert reports, and any orders or requests of the Court, and/or are necessary to respond to the evidence presented by Defendants at trial.

B. Plaintiffs intend to prove the following contested facts with regard to damages:

Not applicable at this time. Plaintiffs reserve the right to offer evidence in support of a damages award if circumstances change.

TAB 7

7. DEFENDANTS' CONTESTED FACTS (Proof shall be limited at trial to the matters set forth below. Failure to set forth any matter shall be deemed a waiver thereof.)

A. **Defendants intend to prove the following contested facts with regard to liability:**

In an effort not to overburden the Court with a voluminous submission of Contested Facts at this pre-trial stage, Defendants have attempted to streamline their Contested Facts. Defendants reserve the right to expound upon and/or provide additional detail, as necessary, to further support Defendants' positions at trial, as well as Defendants' pretrial brief. In view of the foregoing, Defendants incorporate by reference their experts' reports and the documents cited therein in full.

Finally, and for the avoidance of any doubt, Defendants dispute and reserve all rights to introduce evidence and argument rebutting the statements set forth in Plaintiffs statement of Contested Facts (Tab 6) and statement of Legal Issues discussed *infra*, (Tab 18).

PROPOSED PRETRIAL ORDER

DEFENDANTS' CONTESTED FACTS

Defendants Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc. (collectively, "Torrent") together with Defendant Indoco Remedies Ltd. ("Indoco") (collectively with Torrent, "Defendants") submit the following statement of contested facts that remain to be litigated at trial ("Statement"). To the extent that a contested fact in one section may be considered a contested fact in another section, respectively, they are to be considered as such. Headings and subheadings are for organizational purposes only, not an admission that any facts under a particular heading are relevant only to that section.

Defendants reserve the right to modify or amend this Statement to the extent necessary to reflect any future rulings by the Court, and to supplement or amend this Statement to fairly respond to any new issues that Plaintiffs may raise. To the extent Defendants' statement of legal issues that remain to be litigated (Tab 19) contain contested issues of fact, those contested issues of fact are hereby incorporated by reference. Moreover, if any contested facts identified below should properly be considered a legal issue, then such statement should be considered to be part of Defendants' statement of legal issues that remain to be litigated at trial (Tab 19)

Finally, as Defendants indicated in the main body of the pretrial order, Defendants incorporate by reference their expert reports and interrogatory responses in support of any proof to be presented by expert testimony that Defendants will offer to establish the invalidity of U.S. Patent No. 7,807,689 (the "'689 patent") at trial and/or in rebuttal to any allegations that Plaintiffs present at trial. As a result, the contested facts presented below are a mere summary of the contested facts that Defendants intend to litigate at trial and are not intended to be exhaustive. Defendants specifically reserve the right to expound upon and/or provide additional detail and

facts, as necessary, to further support Defendants' intended proofs at trial. Defendants' statement of claims and affirmative defenses they intend to prove at trial is submitted as Tab 9.

I. BACKGROUND

A. THE PATENT-IN-SUIT AND CLAIMS

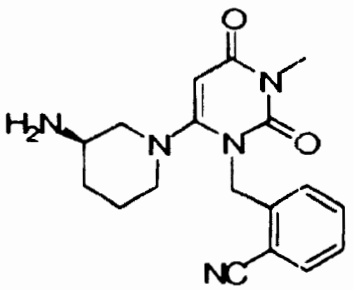
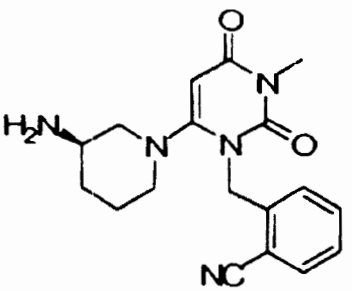
1. The asserted claims

1. Plaintiffs have asserted independent claims 4 and 12 of the '689 patent against Defendants.[1]

2. For purposes of this litigation, the priority date of the '689 patent is November 18, 2004.

3. The asserted claims are directed to a specific DPP-IV inhibitor compound known as Alogliptin (or a salt form thereof).

4. The asserted claims of the '689 patent, as corrected by a Certificate of Correction dated March 20, 2012, are reproduced in table form below.

Claim 4 of the '689 Patent	**Claim 12 of the '689 Patent**
A compound of the formula  or pharmaceutically acceptable salts thereof	A compound of the formula  wherein the compound is present as a benzoate salt.

[1] Plaintiffs originally asserted claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent; claims 2-3, 5-7, 9, 11, 15, and 18 of U.S. Patent No. 8,288,539; and claims 1, 4, 6-8, 10, 12, 14-17, 19-21, 27 and 29 of U.S. Patent No. 8,173,663 against Defendants in this action. Plaintiffs, however, in their recently denied Motion for Summary Judgment of Infringement and Validity stated that "Takeda intends to move forward in this litigation only on these two claims." [ECF No. 93 at 1.] Claims 4 and 12 of the '689 patent are therefore the only asserted claims that remain in the litigation.

5. The compound claimed in claim 4, Alogliptin, and its benzoate salt form in claim 12, are for use as a DPP-IV inhibitor to treat type 2 diabetes, as discussed in the specification of the '689 patent (and the packaging insert of Nesina®).

6. The '689 Patent is entitled "Dipeptidyl Peptidase Inhibitors" and therefore confirms that any compounds disclosed or claimed therein must be a dipeptidyl peptidase inhibitor, such as a DPP-IV inhibitor.

7. The '689 patent specification discloses that the "present invention relates to compounds that have activity for inhibiting DPP-IV." ('689 patent, col. 3:61-62). The '689 patent specification further discloses that "[o]ne set of indications that DPP-IV inhibitors of the present invention may be used to treat are those involving the prevention and treatment of diabetes and obesity, in particular type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT) . . . ." ('689 patent, col. 49:6-12).

II. THE PERSON OF ORDINARY SKILL IN THE ART ("POSA")

8. According to Defendants' expert Dr. Rotella, a POSA with respect to the subject matter of the '689 patent would have a Ph.D. or an equivalent advanced degree in medicinal and/or organic chemistry (or a closely related discipline such as pharmaceutical chemistry), having at least several years of relevant practical academic or industrial experience researching and developing drugs for treating type 2 diabetes.

9. According to Defendants' expert Dr. Ferraris, a POSA with respect to the subject matter of the '689 patent would have a Ph.D. or an equivalent advanced degree in medicinal chemistry and/or organic chemistry (or a closely related discipline such as pharmaceutical chemistry), having at least several years of relevant practical academic or industrial experience researching and developing drugs and can use knowledge in organic chemistry for designing and synthesizing small molecule drugs such as antidiabetic drugs for treating type 2 diabetes.

10. Dr. Nichols lacks the requisite experience and qualifications to meet the definition of a POSA as defined by Defendants' experts above, and as admitted by Dr. Nichols during his deposition.

11. Defendants' experts' definition of a POSA is the correct definition of a POSA as it stays true to the subject matter of the '689 patent.

12. Plaintiffs' expert, Dr. Nichols, overstates the level of unpredictability in the field of medicinal chemistry as it relates to DPP-IV and its inhibitors, as well as the requirement for an understanding of the specific structure-activity relationships for certain specific compounds.

13. Prior to 2004, the POSA would have readily known that the crystal structure of DPP-IV was disclosed and that such a structure could be used in the design, identification, and evaluation of potential non-peptidic DPP-IV inhibitors.

14. Specifically, the POSA would have known and understood that the overall key interactions and binding properties with the DPP-IV enzyme (for example, key interactions with S1, S2 binding pockets) and a peptidic-like substrate inhibitor are similar and can be used to design, identify, and/or evaluate potential *non-peptidic* inhibitors.

15. Prior art references such as Lambeir 2003 support that a POSA would have known that the interaction regions and binding properties between peptide-like DPP-IV inhibitors and non-peptidic inhibitors are similar.

16. No prior art references suggest that the binding sites on DPP-IV are entirely different between peptide-like DPP-IV inhibitors and non-peptidic inhibitors.

17. Therefore, prior to March 2004, it would have been routine and obvious for a POSA to rely on the teachings about the general interactions and binding properties from crystal structure information from DPP-IV and the substrate/inhibitor DPP-IV complexes to design,

search, and identify with a reasonable expectation of success potential non-peptidic DPP-IV inhibitors (e.g., non-peptidic DPP-IV inhibitors where uracil was the scaffold).

The POSA, prior to March 2004, would have also relied on computer-aided modeling to evaluate and/or further optimize potentially new non-peptidic DPP-IV inhibitor compounds with new scaffolds (e.g., uracil) to determine whether the potentially new-non-peptidic DPP-IV inhibitor would have more favorable binding properties with the DPP-IV enzyme and more potency than the lead compound that is being modified to include a new scaffold.

III. THE ASSERTED CLAIMS ARE INVALID UNDER OBVIOUSNESS-TYPE DOUBLE PATENTING

18. Claims 4 and 12 of the '689 patent are invalid for obviousness-type double patenting over claim 162 of U.S. Patent No. 7,723,444 (the "Feng patent") in view of Kim et al., "Anti-diabetic activity of Constituents of Lycii Fructus," The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("Kim 1998") and the common knowledge of a POSA as set forth in the expert reports of Dr. David P. Rotella.

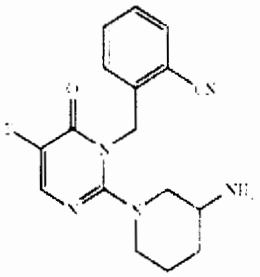
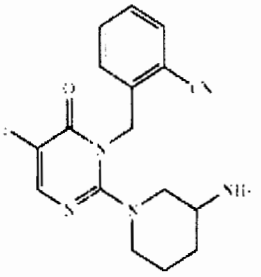
A. The Feng Patent

19. The Feng patent issued on May 25, 2010 and is an invalidating reference under the judicially created doctrine of obviousness-type double patenting because it along with the '689 patent share a common assignee (Takeda Japan).

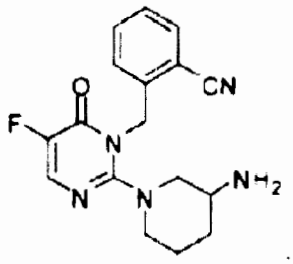
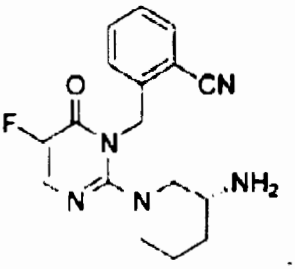
20. The Feng patent discloses a starting DPP-IV inhibitor compound (i.e., a "lead compound") in claim 162 that is not patentably distinct from asserted claims 4 and 12 of the '689 patent.

21. The Feng patent issued with a ministerial error in claim 162 because it failed to show the proper stereochemistry for the 3-aminopiperidinyl substituent. This is evidenced by the fact that the compound structures in claim 161 and claim 162 of the Feng patent are *identical*, which a POSA would know could not be right. (*See* Sep. 13, 2019 Nichols Dep. Tr. at 107:4-9

where Dr. Nichols admitted that given the identical nature of the compounds there probably is a "mistake there.")

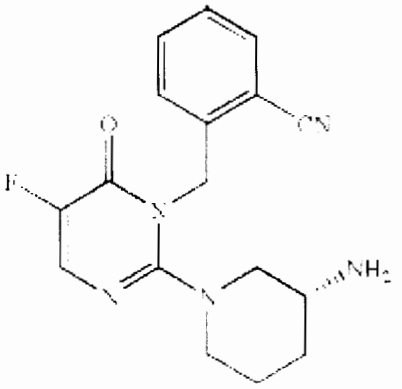
Claim 161 of U.S. Patent No. 7,723,344	**Claim 162 of U.S. Patent No. 7,723,344**
A compound having the formula: 	A compound according to claim 161 having the formula: 

22. According to U.S. Application No. 10/918,327 ("the '327 Application") which Feng 2010 issued from, claim 162 was to have the correct stereochemistry for the 3-aminopiperidinyl substituent. This can be seen from the table below comparing claim 235 from the '327 Application which issued as claim 161 in the Feng patent and claim 236 which ultimately issued as claim 162 in the Feng patent without the correct stereochemistry.

Claim 235 from '327 Application	**Claim 236 from '327 Application**
A compound having the formula: 	A compound according to claim 235 having the formula: 

23. In addition, nearly all 36 examples (except only a few examples that did not specify a stereoisomer of the compound) disclosed in the specification of the Feng patent specify the (*R*)-enantiomer of the 3-aminopiperidinyl group rather than the (*S*)-enantiomer.

24. Therefore, claim 162 from the Feng patent would have readily been understood by a POSA to recite "[a] compound according to the claim 161" having the below structure as originally included in pending claim 236 (i.e., a chemical structure showing the (*R*)-enantiomer for the 3-aminopiperidiyl group).



B. Kim 1998

25. Kim 1998 is prior art to the '689 patent under 35 U.S.C. 102(b) because it was published more than one year prior to the earliest filing date to which the '689 patent can claim priority.

26. A POSA would have been aware of Kim 1998 and utilized its teachings to develop DPP-IV inhibitors for the treatment of type II diabetes.

27. Kim 1998 relates to the subject matter of the '689 patent because it discloses a study in which the anti-diabetic effects of four constituents of Lycci Fructus (uracil, rutin, betanine, and ascorbic acid), along with the commercially available anti-diabetic medication Daonil®, were tested on streptozotocin-induced diabetic rats.

28. Kim 1998 discovered that uracil's blood glucose inhibition rate was much higher than the commercially-available anti-diabetic medication, Daonil®.

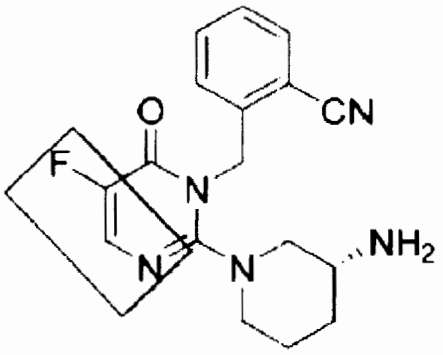
29. Kim 1998 concluded as a result of the study that uracil "demonstrate[d] significant anti-diabetic effects, suggesting [its] potential [use] as [a] new diabetes treatment."

30. Although, rutin and ascorbic acid had blood glucose inhibition rates higher than Daonil® as well, the POSA would have only considered uracil as a potential scaffold or core for use in a novel DPP-IV inhibitor given its simple shape and size and Kim 1998's conclusion that uracil could be used as a new diabetes treatment.

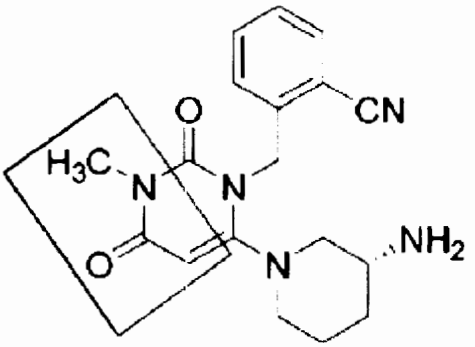
C. Claims 4 and 12 of the '689 Patent are Not Patentably Distinct from Claim 162 of the Feng Patent in view of Kim 1998

31. A side-by-side comparison of claim 162 from the Feng patent (i.e., the lead compound) with the structure of *R*-Alogliptin as claimed in claims 4 and 12 confirms that Alogliptin is nothing more than a slight modification of the lead compound in claim 162.

Claim 162 Compound



***R*-alogliptin**



32. The double-patenting analysis comes down to essentially one question: whether a POSA based on the Claim 162 Compound (i.e., the lead compound) would have found it obvious

to make a modification that entails replacing in the lead compound the "pyrimidinone-structure core with a fluorine at the N3 position" with a "uracil-structure core with a methyl group" in light of the prior art.

33. Replacing the Claim 162 Compound's "pyrimidinone-structure core with a fluorine at the N3 position" with a "uracil-structure core with a methyl group" would have been a logical, routine, and obvious modification based on the teachings in Kim 1998 and the common knowledge in the art.

34. Replacing core scaffolds in one compound with another scaffold (i.e., "scaffold replacement") to develop (1) novel drugs and (2) drugs with improved binding affinity to a particular target protein (e.g., DPP-IV) was well-known in the art, especially at the time of the claimed invention.

35. The scaffold replacement method was the same method used by the inventors of the '689 patent to arrive at the claimed compound of Alogliptin. .

36. Use of the scaffold replacement method would have been used by a POSA in the instant case given that the crystal structure of human DPP-IV was already disclosed in the prior art.

37. With the crystal structure of DPP-IV already disclosed in the prior art, the POSA would have easily been able to predict with a reasonable expectation of success whether a new and similar scaffold, such as uracil, would have improved binding affinity over the previous scaffold (e.g., Claim 162 Compound's pyrimidinone-structure core/scaffold) with the DPP-IV target protein.

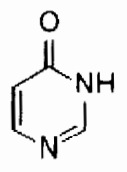
38. The POSA would have been motivated to only modify the scaffold/core of the Claim 162 Compound and not the 2-cyanobenzyl and 3-aminopiperidinyl substituents or their locations on the scaffold because (1) removing or altering the location of the 2-cyanobenzyl and

3-aminopiperidinyl substituents when modifying the Claim 162 Compound would potentially cause the resulting compound to have no DPP-IV inhibition activity and (2) several prior art references teach DPP-IV inhibitors with both 2-cyanobenzyl and 3-aminopiperidinyl groups.

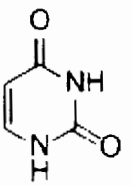
39. In view of the POSA's motivation to only modify the "pyrimidinone-structure core" of the Claim 162 compound (and not the substituents), the POSA, having knowledge of the all the pertinent prior art, would have naturally replaced Claim 162 Compound's "pyrimidinone-structure core" with a uracil core because Kim 1998 disclosed that uracil has significant antidiabetic activity with respect to Type 2 Diabetes and potential to be used as a new diabetes treatment.

40. Additional reasons for why a POSA would have then been motivated to replace Claim 162 Compound's "pyrimidinone-structure core" with the uracil core as disclosed in Kim 1998 is because several prior art references also disclose uracil as being part of bicyclic scaffolds used in DPP-IV inhibitors (e.g., Kanstrup 2003).

41. The POSA would have also been additionally motivated to replace Claim 162 Compound's "pyrimidinone-structure core" with the uracil core as disclosed in Kim 1998 because (as demonstrated below) uracil is similar in shape and size as Claim 162 Compound's "pyrimidinone-structure core" and therefore can bind to the hydrophobic S2 pocket of DPP-IV in essentially the same way as the Claim 162 compound.



pyrimidinone

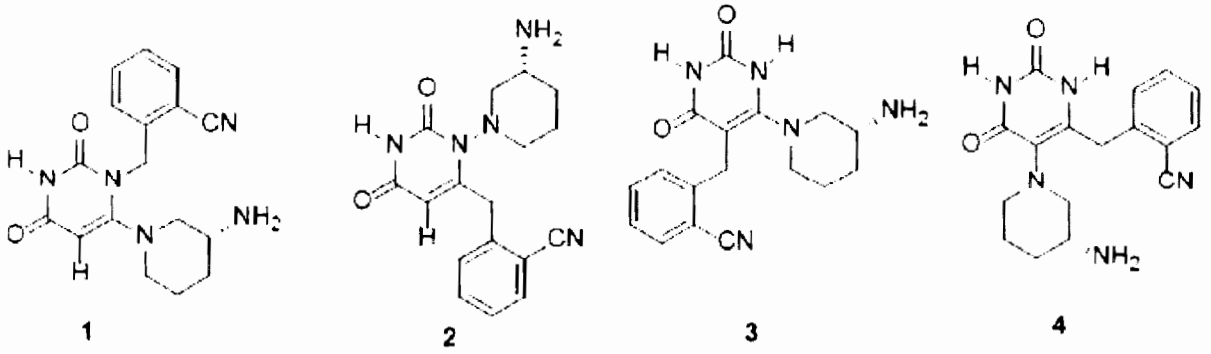


uracil

42. Therefore, given that the POSA's goal is to develop novel, highly specific, potent, and simple DPP-IV inhibitors for the treatment of type 2 diabetes, it would have been a natural

and obvious choice for POSA to replace the pyrimidinone scaffold in the Claim 162 Compound with a pyrimidinedione scaffold (i.e., uracil core) as informed by Kim 1998 and the common knowledge in the art.

43. When replacing Claim 162 Compound's "pyrimidinone-structure core" with a uracil core as informed by Kim 1998 and the common knowledge in the art, the POSA would have ultimately arrived at the four Uracil-based analogues reproduced below:



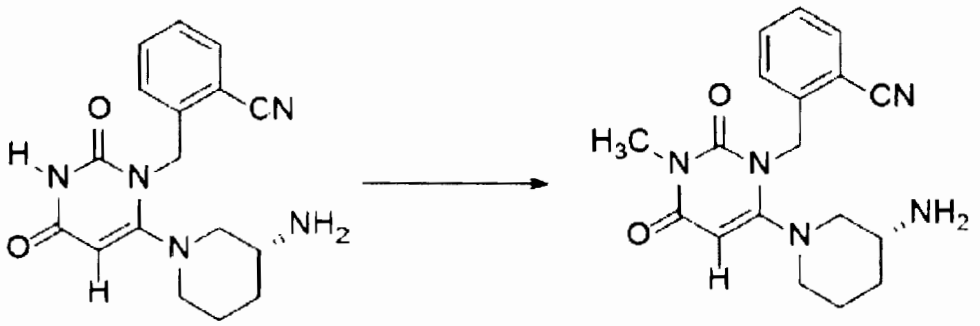
44. The POSA would have prioritized Uracil analogue (1) for further optimization due to Uracil analogue (2) containing a hydrazine bond (i.e., a nitrogen tipple bonded to a nitrogen) and Uracil analogues (3) and (4) containing spatial arrangements of the 3-aminiopiperidinyl and 2-cyanobenzyl that were not similar to the orignal Claim 162 Compound in the Feng patent.

45. It would have also been routine experimentation for the POSA to also use computer aided modeling to confirm that Uracil analogue (1) had the best potential to interact favorably with the S1 and S2 pockets of DPP-IV when compared to Uracil analogues (3) and (4).

46. A POSA without the benefit of Kim 1998, but with the common knowledge of the art, would have also separately arrived at Uracil analogue (1) with a reasonable expectation of success by simply replacing the fluoroolefin moiety in the pyrimidinone-structure core of the Claim 162 Compound with an amide bond.

47. Prior to 2004 it was commonly known in the art that a fluoroolefin mimics an amide bond, and therefore the replacement of the fluoroolefin moiety with an amide bond would naturally result in a novel and active DPP-IV inhibitor. For example, Lambier 2003 and Welch 1998, which were published more than one year prior to the priority date of the '689 patent and are therefore 35 U.S.C. §102(b) references, proved this well-known fact that fluoro-olefin mimics an amide bond in DPP-IV inhibitors.

48. Whether the POSA arrived at Uracil analogue (1) through the scaffold replacement method or the fluoroolefin method, the POSA seeking to further optimize Uracil analogue (1) to ensure that the resulting DPP-IV inhibitor would have the best potency and selectivity would have also been motivated to replace the N3-hydrogen substituent in analogue (1) with a small hydrophobic group such as methyl (the smallest alkyl group) to better occupy the hydrophobic S2 pocket of DPP-IV. This routine substitution would have resulted in Alogliptin, as shown below:



49. For these reasons, it would have been obvious for a POSA who is seeking to develop a novel, highly specific, and potent DPP-IV inhibitor for the treatment of type 2 diabetes, to replace the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil) either through the commonly practiced scaffold

replacement method or fluoro-olefin method to arrive at the *R*-Alogliptin compound claimed in claims 4 and 12 with a reasonable expectation of success. Doing so would have been a matter of routine experimentation and optimization of a POSA in the art.

50. Regarding claim 12's requirement that the Alogliptin compound be in the form of a benzoate salt, it was well-known in the art that the benzoate salt form is a salt form that has been commonly used in the pharmaceutical field.

51. At the time of the invention there were only 53 FDA approved acid addition salt forms—one of which was the benzoate salt form.

52. Kanstrup 2003, a reference that discloses non-peptidic DPP-IV inhibitors, additionally disclosed that benzoate may be used as the salt form for the DPP-IV inhibitors disclosed therein.

53. The POSA would have started with the salt forms that have been used with non-peptidic DPP-IV inhibitors in searching for a suitable salt for alogliptin.

54. Therefore, it would have been obvious for a POSA to make the benzoate salt form of Alogliptin

IV. THE ASSERTED CLAIMS ARE INVALID FOR BEING OBVIOUS UNDER 35 U.S.C §103

55. Claims 4 and 12 of the '689 patent are invalid for obviousness under 35 U.S.C. § 103(a) in view of the prior art and the common knowledge of a POSA. In particular, International Publication WO 2002/068420 (the "WO '420 publication") and its English language equivalent Canadian Patent No. CA 2 435 730 (the "CA '730 patent") as well as International Publication WO 2003/004496 A1 (the "WO '496 publication") (collectively, the "Lead Compound References") all disclose 1,3-dimethyl-7-(2-cyano-benzyl)-8-(3-amino-piperidin-1-yl)-xanthine ("DCAX"), which a POSA would have recognized as a lead compound for further development of a DPP-IV inhibitor.

56. It would have been obvious for a POSA to modify DCAX to form alogliptin,guided by the teachings of the Lead Compound References as well as what wasknown in the art about the structure of DPP-IV and DPP-IVinhibitors (as indicated *inter alia* in the"Structure References") and what was known in the art about scaffold modification (as indicated *inter alia* in the "Substitution References" as well as disclosed as the current state of the art in 2003 by Böhm[2]).

57. The choice of the R enantiomer of alogliptin and the development of the benzoate salt of alogliptin also would have been obvious given what was known in the art regarding the importance of evaluating enantiomers in medicaments (as indicated *inter alia* in the "Stereoisomer References") and the benefits of pharmaceutical salts to pharmaceutical compounds (as indicated *inter alia* in the "Salt References"), as well as based on the explicit teachings of the WO '496 publication, which discloses the R enantiomer of DCAX and specifically suggests a limited number of salts for formulation that includes benzoic acid salts.

A. Lead Compound References

1. The WO '420 publication/CA '730 patent

58. International Publication WO 2002/068420 A1, Xanthine Derivatives, Production and Use Thereof As Medicament, was filed February 21, 2002, and published September 6, 2002 (the "WO '420 publication"). Canadian Patent No. CA 2 435 730, Xanthine Derivatives, The

[2] Böhm, et al., *Scaffold Hopping*, 1(3) DRUG DISCOVERY TODAY 217-224 (Dec. 2004). While Böhm was published in December 2004, the reference reviews examples of scaffold modification prior to that date and thus provides evidence of the knowledge that one of ordinary skill in the art would have had at the time of the patent filings at issue in this case. *See, e.g., Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031 (Fed. Cir., 2018)("The Board has recognized that non-prior art evidence of what was known "cannot be applied, independently, as teachings separately combinable" with other prior art, but "can be relied on for their proper supporting roles, e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have under-stood a prior art disclosure."); MPEP 2124 (*citing Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992))("References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made.").

Preparation Thereof and Their Use As Pharmaceutical Compositions, (the "CA '430 patent"), issued from the National Phase Application of PCT Application No. PCT/EP2002/001820 (published as WO'420), and is the English language equivalent to the WO '420 publication. Each of the patents is assigned to Boehringer Ingelheim.

59. The WO '420 publication and the CA '730 patent are prior art references under 35 U.S.C. § 102(b).

60. The WO '420 publication and CA '730 patent are directed to substituted xanthines that exhibit inhibition of DPP-IV. The reference describes that the compounds have use in preventing or treating, in particular, type I or type II diabetes mellitus. The reference also describes converting the compounds into salts.

61. Among 31 compounds whose biological properties were investigated using a DPP-IV assay, Compound 1(121) (*i.e.*, DCAX) was found remarkably high in potency.

2. The WO '496 publication

62. International Publication WO 2003/004496 A1, DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes, was filed June 27, 2002 and published January 16, 2003 (the "WO '496 publication"). The WO '496 publication is assigned to Novo Nordisk.

63. The WO '496 publication is a prior art reference under 35 U.S.C. § 102(b).

64. The WO '496 publication describes purine derivatives useful for treating diseases "such as type 2 diabetes."

65. The WO '496 publication provides, as its very first example (Example 1), the xanthine derivative identical to DCAX.

66. The WO '496 publication further provides as an example the R enantiomer of DCAX and suggests the use of benzoic acid for the development of pharmaceutical salts.

67. A POSA would have been aware that both Boehringer Ingelheim and Novo Nordisk were independently pursuing xanthene derivative compounds as DPP-IV inhibitors, and that certain of those compounds were highly potent. A POSA further would have recognized that both companies specifically disclosed DCAX, a highly potent DPP-IV inhibitor.

68. as This observation provides a strong suggestion that such a compound can form a starting point of further research and development efforts. Therefore, a POSA would have chosen DCAX as a lead compound.

B. DPP-IV Inhibitor Structure References

69. One of ordinary skill in the art as of March 2004 would also have been aware of the extensive research that had taken place to identify key structural components necessary for DPP-IV inhibitors. Such references are set forth below.

1. Evans

70. Evans, D., Dipeptidyl peptidase IV inhibitors, 5(6) IDrugs 577-585 (June 2002) ("Evans") is a prior art reference under 35 U.S.C. § 102(b).

71. Evans reviews the patent literature from January 2001 to May 2002, noting that there "has been increased interest in DPP-IV inhibitors since their potential for the treatment of diabetes was identified." The "review focuses on reversible inhibitors" useful "in the treatment of Type II diabetes," and covers both "dipeptide-like inhibitors that mimic the preferred substrates" and "non-peptide inhibitors."

72. Evans also discloses that the use of "DPP-IV inhibitors has been proposed as a possible treatment of Type II diabetes." Evans specifically recognizes that "[t]he cyano group is sufficiently electrophilic to interact with the serine hydroxyl, but does not cause stability problems" in reviewing a series of dipeptide-based inhibitors. Non-peptide inhibitors also contain this group.

73. Evans further discloses that a DPP-IV inhibitor should include an N-terminal primary or secondary amine and that such a group was essential.

2. *Wiedeman*

74. Wiedeman, P. et al., Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes, 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003) ("Wiedeman") is a prior art reference under 35 U.S.C. § 102(b).

75. Wiedeman summarizes "advances in the design of potent and selective small molecule inhibitors of DPP-IV", and challenges for the development of DPP-IV inhibitors for treating "impaired glucose tolerance" and type II diabetes. Wiedeman explains that providing GLP-1 itself as a treatment for type II diabetes is "impractical" because of its short 1 minute to 1.5 minute half-life. Wiedeman provides a summary of studies underway for certain DPP-IV inhibitors, including a study in human type 2 diabetics, all of which showed improved glucose tolerance.

76. Among non-peptidic molecules as DPP-IV inhibitors, Wiedeman highlights xanthines as having "attracted attention." The reference then specifically notes that "[t]wo companies," Novo Nordisk and Boehringer Ingelheim, "seem to have independently discovered this class of inhibitors." Wiedeman favorably describes the bioavailability and potency of such compounds.

77. Wiedeman also makes reference to structure biology of the DPP-IV enzyme. Among other things, Wiedeman discloses that Glutamic acid residues 205 and 206 of the DPP-IV target form a salt bridge to an amine group in the inhibitor.

3. *Lambeir*

78. Lambeir, A., Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV, 40(3) Crit. Rev.

Clin. Lab. Sci. 209-294, 216 (Jun. 2003) ("Lambeir") is a prior art reference under 35 U.S.C. § 102(b).

79. Lambeir provides a summary on the DPP-IV enzyme, including its amino acid sequence, structural characteristics, and role in type 2 diabetes. Lambeir identifies the increase in affinity with the use of a cyano group in DPP-IV inhibitors.

80. 97. Lambeir also discloses that catalysis by DPP-IV is "strongly stereospecific," requiring specific configurations for activity.

81. Lambeir identifies problems such as instability, toxicity, lack of selectivity, hydrolysis by DPP-IV or weak inhibition associated with the peptide DPP-IV inhibitors

4. *Engel*

82. Engel, M., et al., The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism, 100(9) PNAS 5063-068 (Apr. 29, 2003) ("Engel") is a prior art reference under 35 U.S.C. § 102(b).

83. Engel describes the crystal structures of DPP-IV and its structural features that underlie the substrate recognition and binding of DPP-IV. Engel discloses the crystal structure of DPP IV enzyme, and discusses the active and non-active site-directed inhibition strategies of the DPP IV target. Determination of DPP-IV crystal structure and identification of important elements of DPP-IV active site provides an excellent starting point for rational design of DPP-IV inhibitors.

5. *Aertgeerts*

84. Aertgeerts, K., et al., Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation, 13(2) Protein Sci. 412-421 (Feb. 2004) ("Aertgeerts") is a prior art reference under 35 U.S.C. § 102(a).

85. Aertgeerts reports the crystal structure of DPP-IV in its free form and in complex with part of a substrate (Neuropeptide Y) known to be involved in the regulation of insulin release.

86. In describing the DPP-IV enzyme structure, Aertgeerts identifies a hydrophobic S1 pocket and an S2 hydrophobic pocket. As in the Evans reference, Aertgeerts identifies a serine hydroxyl group in S1 that is essential for activity, noting that the group moves significantly to interact with the substrate. For the S2 pocket, Aertgeerts explains that the site "preferentially recognizes large hydrophobic and aromatic side chains." (Aertgeerts at 417.) Knowledge of the DPP-IV/substrate structure provides guidance for rational design of highly specific and potent inhibitors of DPP-IV that can be used for the treatment of diabetes and related disorders.

87. Aertgeerts also notes that DPP-IV inhibitors are currently under investigation in human trials for treating type II diabetes. The reference explains the role of DPP-IV in regulating plasma glucose levels by control of GLP-1.

C. Substitution References

88. A number of references also would have provided motivation for one of ordinary skill in the art to change the core of the compound identified in the '420 publication/CA '730 patent and the WO '496 publication to the core of alogliptin.

1. *The '051 patent*

89. U.S. Patent No. 5,142,051, "N-Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity," filed July 17, 1987 and issued Aug. 25, 1992 (the "'051 patent") is a prior art reference under 35 U.S.C. § 102(b).

90. In discussing the interchangeability of certain heterocyclic compounds, the '051 patent discloses, "[t]he heterocyclic base in compounds of the general formula I may be not only a so-called natural pyrimidine or purine base (uracil, thymine, cytosine, guanine, adenine, hypoxanthine, xanthine) or its substituted derivative, but also a modified base such as an aza, deaza, deoxy or deamino analogue, a 6-alkylpurine, etc."

2. The '476 patent

91. U.S. Patent No. 5,780,476, "Hydroxyl-Containing Xanthine Compounds," filed June 6, 1995, and issued July 14, 1998 (the "'476 patent") is a prior art reference under 35 U.S.C. § 102(b).

92. According to the '476 patent, "[p]referred ring cores include substituted or unsubstituted glutarimide, methylthymine, methyluracil, thymine, theobromine, uracil and xanthine. Exemplary preferred cores include, but are not limited to: 1,3-cyclohexanedione, 1,3-cyclopentanedione; 1,3-dihydroxynaphthalene; 1-methyllumazine; methylbarbituric acid; 3,3-dimethylflutarimide; 2-hydroxypyridine; methyldihydroxypyrazolopyrimidine (preferably, 1,3-dimethyldihydroxypyrazolo[4,3-d] pyrimidine); methylpyrrolopyrimidine (preferably, 1-methylpyrrolo [2,3-d] pyrimidine); 2-pyrrole amides; 3-pyrrole amides; 1,2,3,4-tetrahydroisoquinolone; 1-methyl-2,4(1H,3H)-quinazolinedione (1-methylbenzoyleneurea); quinazolin-4(3H)-one; alkyl-substituted (C1-6) thymine; methylthymine; alkyl-substituted (C.sub.1-6) uracil; 6-aminouracil; 1-methyl-5,6-dihydrouracil; 1-methyluracil; 5- and/or 6-position substituted uracils; 1,7-dimethylxanthine, 3,7-dimethylxanthine; 3-methylxanthine; 3-methyl-7-methylpivaloylxanthine; 8-amino-3-methylxanthine; and 7-methylhypoxanthine." (See '476 patent at col. 3, lines 4-22.)

3. Davies

93. Davies, T.G., et al., Structure-based design of cyclin-dependent kinase inhibitors, 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002) ("Davies") is a prior art reference under 35 U.S.C. § 102(b).

94. Davies determines that knowledge of the structure of Cyclin dependent Kinase 2 (CDK2) target is key in the design and development of a large number of potent inhibitors. Davies has demonstrated that knowledge of pattern of hydrogen bonds between a known compound containing a purine core and the hinge region of the target can be used to design a new compound containing pyrimidine as the core by recreating the hydrogen bonding in pyrimidine system. The pyrimidine compounds showed more potency than the lead purine compound. (Davies at 127)

D. Stereoisomer References

95. The Lead Compound References explicitly cover stereoisomers. There are also many references that disclose the benefits of single stereoisomers in pharmaceutical drugs as well as the use of mixed enantiomer compounds.

1. *Campbell*

96. Campbell, D.B., Stereoselectivity in Clinical Pharmacokinetics and Drug Development, 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990) ("Campbell") is a prior art reference under 35 U.S.C. § 102(b).

2. *Hutt*

97. Hutt, A.J., The Development of Single-Isomer Molecules: Why and How, 7(4 supp. 1) CNS Spect. 14-22 (2002) ("Hutt") is a prior art reference under 35 U.S.C. § 102(b).

3. *Crossley*

98. Crossley, R., Chirality and the Biological Activity of Drugs, CRC Press (1995) ("Crossley") is a prior art reference under 35 U.S.C. § 102(b).

4. *Izumi*

99. Izumi, T., et al., Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data, 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997) ("Izumi") is a prior art reference under 35 U.S.C. § 102(b).

E. Salt References

100. The Lead Compound references disclose salts of the compounds described, including, in the WO '496 publication, salts relating to benzoic acid.

101. 113. The seminal teaching on pharmaceutically acceptable salts is that of Berge, set forth below. In addition, in March 2004, one of ordinary skill in the art also would have been well aware of how to efficiently develop and analyze pharmaceutical salts as indicated in Higgins below.

1. *Berge*

102. Berge, S.M., et al., Pharmaceutical Salts, 66(1) J. Pharm. Sci.,. 1-19 (Jan. 1977) ("Berge") is a prior art reference under 35 U.S.C. § 102(b).

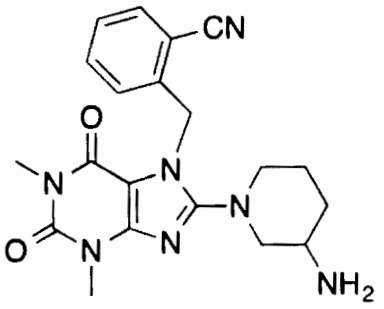
2. *Higgins*

103. Higgins, J.D. & Rocco, W.L., Pharmaceutical Preformulation, Today's Chemist at Work 22-26 (July 2003) ("Higgins") is a prior art reference under 35 U.S.C. § 102(b).

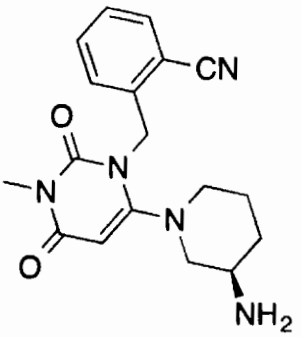
F. Claims 4 and 12 of the '689 Patent are Obvious Under 35 U.S.C. § 103(a) over WO '420 publication/CA '730 patent or WO '496 publication in view of the common knowledge of a POSA

104. It would have been obvious for a POSA to choose DCAX as a lead compound and modify the compound in to arrive at the claimed compound of Alogliptin in claims 4 and 12 with a reasonable expectation of success.

105. A side-by-side comparison DCAX (*i.e.*, the lead compound) with the structure of Alogliptin as claimed in claims 4 and 12 confirms that Alogliptin is nothing more than a slight modification of the lead compound.



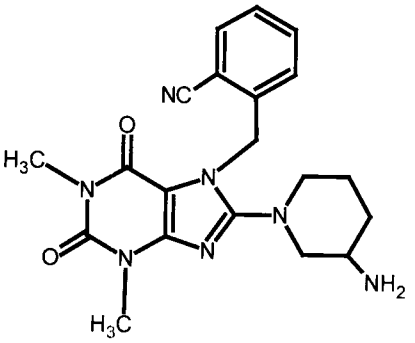
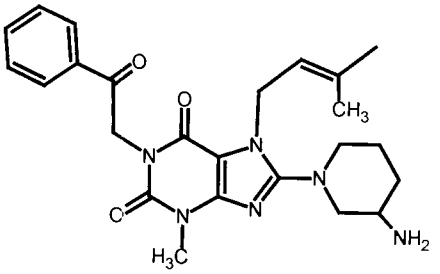
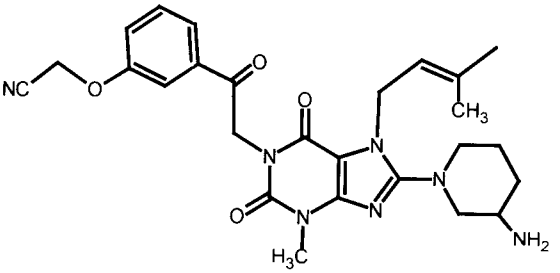
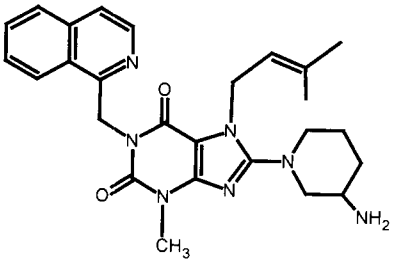
DCAX (Lead Compound)



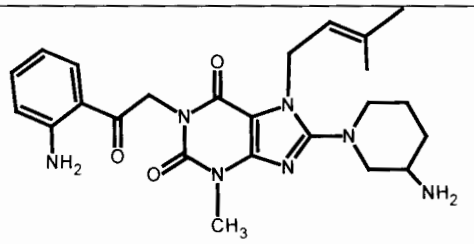
Alogliptin

106. As indicated above, DCAX and Alogliptin are quite similar. The similarities include: (i) a cyanobenzyl group (shown in red) – this group is bound to the nitrogen atom of the central core in both compounds; and (ii) a 3-amino piperidine (shown in blue) – this moiety is bound to the carbon adjacent to the cyanobenzyl group in both compounds.

107. The CA '730 patent also discloses the results obtained from testing 31 compounds for their ability to inhibit DPP-IV activity. Based on the IC50 data reported in the CA '730 patent, 5 test compounds are found to exhibit DPP-IV inhibitory activity in IC50 value ranging between 2 nM and 10 nM indicative of the compounds being highly potent DPP-IV inhibitors. The five compounds identified by their chemical names and respective structures are set forth in the following table together with their IC50 values.

Compound	IC50[3]	Structure
Compound 1(121): 1,3-dimethyl-7-(2-cyano-benzyl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 197:13)	10 nM	
Compound 2(28): 1-(2-phenyl-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 204:24-25)	5 nM	
Compound 2(88): 1-[2-(3-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 214:26-27)	6 nM	
Compound 2(119): 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 220:6-7)	2 nM	

[3] The IC50 data is found in CA '730 patent at cols. 99-100.

Compound	IC50[3]	Structure
Compound 2(136): 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-aminopiperidin-1-yl) xanthine (CA '730 patent, Col. 223:14-15)	3 nM	

108. The highly potent DPP-4 inhibitors set forth in the above table have common structural features. All of the five compounds contain methyl and 3-amino-piperidinyl substituents at positions 3 and 8 of the central xanthine scaffold respectively. Four of the five compounds contain a 3-methyl-2-buten-1-yl group at position 7 of the xanthine scaffold, with one compound, 1(121), containing 2-cyanobenzyl at the corresponding position of the xanthine scaffold.

109. Given the usefulness of DPP-IV inhibitors in the treatment of diabetes mellitus, and the interest in non-peptidic DPP-IV inhibitors containing a xanthine core (Wiedeman at 417), a person of ordinary skill in the art as of March 2004 would have been motivated to consider the five highly potent DPP-IV inhibitors of the CA '730 patent as potential lead compounds.

110. From among the five potent DPP-IV inhibitors disclosed in CA '730 patent, however, DCAX would have stood out as an interesting lead to one of ordinary skill in the art for further development of DPP-IV inhibitors for example, because (1) Novo Nordisk also identified the same compound in their development of xanthine core DPP-IV inhibitors, describing it as the first (Example) in the experimental section of their patent application (2) there are several references that provide information about the structural features of a DPP-IV inhibitor,

particularly the P1 and P2 groups that are crucial for the binding affinity of the DPP-IV inhibitor at the active sites of the DPP-IV enzyme.

111. A POSA would further recognize that compound 1(2) (IC50 = 82 nM) in the '730 patent is identical to DCAX except that for the absence of a nitrile. Because compound 1(2) is 8 fold less potent than DCAX, a POSA would hypothesize that the nitrile is absolutely essential to binding, just like so many other DPP-IV inhibitors at the time.

112. In addition, a POSA would know that a primary amine is part of the pharmacophore of DPP-IV inhibitors because DPP-IV cleaves the penultimate peptide bond from the N-terminus of its substrates (all of which have a primary amine at the N-terminus).

113. A POSA would have recognized the xanthine core of DCAX as the least likely to be involved in imparting the desired DPP-IV inhibitory activity of the compound. The benzonitrile (as well as nitriles in general) were already established as part of the DPP-IV pharmacophore as was the primary amine. In addition, a POSA would have known that xanthines were fraught with intellectual property issues, particularly patent protection issues, which a POSA would have considered in designing new drug treatments. Xanthines had been used as a known scaffold for decades and were very common in a variety of drug discovery projects (including development as phosphodiesterase inhibitors, antimicrobial agents, antitumor agents, etc.).

114. One of ordinary skill in the art would thus retain the cyano-containing moiety and the 3-amino-piperidinyl moiety of DCAX, and would look to modify DCAX by focusing on changing the xanthine scaffold. Scaffold hopping was a known and common technique as of

March 2004, as indicated in Böhm.[4] In examining how to alter the xanthine scaffold, substituting a uracil scaffold would have been a very obvious choice.

115. Medicinal chemists tend to look for certain characteristics in a scaffold. Rings keep the substituents in place, but large rings can cause bulkiness. Decreasing the molecular weight of the scaffold is one common goal of lead modification. One of ordinary skill in the art thus would have substituted one ring structure for a two ring structure in DCAX to see if the compound retained its potency and determine whether the two ring structure was essential. If they had done so, they would have arrived at alogliptin.

116. In addition, xanthine is a purine base belonging to a class of nitrogen-containing bases. In considering modification of the DCAX, one of ordinary skill in the art would naturally consider replacing xanthine with other nitrogen-containing bases. The usefulness of xanthine and uracil scaffolds in pharmaceutical arts was extremely well known at the time. ('051 patent at col. 4, ll. 41-46; '476 patent at col. 2, ln. 5-col. 3, ln. 6.) Because compounds with such scaffolds are similar to naturally occurring bases, they are generally considered as top choices in molecular design.

117. One of ordinary skill in the art also would have been aware that references also teach the substitution of purine bases (one of which is xanthine) with pyrimidine bases (such as uracil) in the design of therapeutically active compounds. ('051 patent at col. 4:41-46; '476

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[4] Böhm teaches that "There are now a large number of tools available" to identify novel compounds with scaffold modifications. Böhm at 223. "The concept of scaffold hopping or bioisoteric replacement is now widely recognized as evident for example by the large number of publications using the word "bioisostere" in the title. Interestingly, some of these tools have been available for more than a decade."

Böhm further discloses examples of such tools:

> We believe that we now witness what could be called a "second wave" of scaffold hopping, driven by a new generation of 3D-structure-literate medicinal chemists, driven by an ever increasing number of available 3D protein structures, access to large databases on successful bioisosteric replacements and also driven by a change in focus away from "holy grail" of peptidomimetic replacement towards more tractable tasks such as the replacement of ring systems with each other.

Id.

patent at col. 2:5-col. 3:6; Davies at 125, 127.) One such reference is Davies. In Davies, structural analysis showed a pattern of hydrogen bonds between the purine ring (central scaffold) of a lead com-pound and the enzyme at issue (cyclin-dependent kinase or CDK). In expanding from the lead compound, researchers recreated the pattern of hydrogen bonds that existed between the purine ring and CDK enzyme using a pyrimidine system. The pyrimidine compounds showed more potency than the lead purine compound.

118. The sole difference between alogliptin and DCAX is the substitution of the xanthine core of DCAX with a uracil/pyrimidine core. Based on the knowledge of one of ordinary skill in the art in March 2004, which included knowledge of the crystal structure of the DPP-IV enzyme and the significance of utilizing the crystal structure in applying structure based drug design, this substitution would have been obvious to one of ordinary skill in the art and/or the '051 patent, the '476 patent, and Davies reference. Thus, based on the structure based drug design approach, using DCAX as a lead compound a medicinal chemist would have expected the resulting compound obtained by substituting the xanthine scaffold of the DCAX with the uracil scaffold to also have DPP-IV inhibitory activity.

119. Claims 4 and 12 of the '689 patent, which cover alogliptin, are obvious based on the WO '420 publication/CA '730 patent (or WO '496, which discloses the same lead compound) in combination with what was known in the art about the structure of DPP-IV inhibitors (Evans, see also Engel and Artgeerts) and what was known in the art about suitable and potentially superior substitutions for xanthine scaffolds (any of the Substitution References, and the '051 patent in particular).

120. A person of ordinary skill in the art would have recognized that alogliptin is a chiral compound and thus has isomeric forms. It was well known as of March 2004 to evaluate stereoisomers of pharmaceutical compounds given that the potency and toxicity of each

stereoisomer may differ. (Campbell, Hutt, Crossley, and Izumi.) The stereospecificity of DPP-IV was also known. (Lambier at 220.)

121. Additionally, the CA '730 patent teaches that the compounds described in the reference (including the DCAX) can be resolved into their enantiomers and/or diastereomers and further discloses some of the known methods in the art for separation and isolation. R-DCAX is also explicitly taught in the WO '496 publication as Example 16. The skilled artisan would be motivated to isolate and test the characteristics of the isomers of alogliptin, including R-alogliptin, to optimize its properties and based on the teachings of the CA '730 patent and the WO '496 publication.

122. By March 2004, a person of ordinary skill in the art would have been aware that certain important characteristics, such as solubility, stability, and the pharmacokinetic profile, of an active free base or acid pharmaceutical compound can be improved by making a salt from the compound.

123. Strategies for developing and selecting suitable pharmaceutical salts were well known and in common use. Drugs in the form of their benzoate salts were known for decades prior to the filing of the '689 patent. (Berge at 2, Table 1). Additionally, high through-put techniques were well known as of March 2004, which enable researchers to efficiently synthesize and analyze dozens of salt forms of pharmaceutical compounds to find the most suitable salt form. This technique and its ubiquity is described in the Higgins reference, for example, at 22, 24.

124. The WO '496 publication directs a POSA to develop pharmaceutical salts, naming benzoic acid explicitly as part of a limited list of just 14 organic acids.

125. One of ordinary skill in the art would have been motivated from the knowledge in the art and teachings such as that found in Berge and Higgins, as well as the direction from the

WO '496 publication, to develop pharmaceutically acceptable salts of alogliptin, including the benzoate salt form. Benzoate salts were known and have also been considered acceptable by the FDA for decades.

V. SECONDARY CONSIDERATIONS

126. Plaintiffs did not meet their burden to present any evidence of secondary considerations of nonobviousness to rebut Defendants' obviousness-type double patenting and 35 U.S.C.§ 103 obviousness arguments.

127. Plaintiffs did not assert commercial success as evidence of a secondary consideration of nonobviousness.

128. Plaintiffs have not adduced any evidence demonstrating that Alogliptin's safety and efficacy were unexpected.

129. A POSA would have expected the xanthine core of DCAX to contribute the least to the binding and inhibition of DPP-IV. Replacing a xanthine with a uracil moiety thus would not have been expected to have a significant negative effect on potency.

130. A POSA equipped with the readily available crystal structure of DPP-IV would have also reasonably expected that the replacement of the pyrimidinone scaffold in the DPP-IV compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil) as informed by Kim 1998, would have resulted in a DPP-IV inhibitor compound having significant inhibition potency and selectivity for DPP-IV.

131. Similarly, the choice of the benzoate salt of Alogliptin in claim 12 was not unexpected. The POSA would have known at the time of the invention that benzoate salt had been used with other non-peptidic DPP-IV inhibitors, particularly as the salt form for the xanthine-based DPP-IV inhibitors with the same side chains as alogliptin. The POSA would

have therefore started with the salts disclosed for use with the xanthine-based DPP-IV inhibitors, which included the benzoate salt.

132. There is nothing in the prior art that taught away from Alogliptin. The cherry-picked statement in Villhauer that Dr. Nichols relies upon to establish a teaching away argument, would not have been considered by a POSA seeking to develop new nonpeptidic small molecule DPP-IV inhibitors. This is because the POSA would have readily recognized that such a statement was made in the context of discussing certain specific "peptide-like inhibitors." A POSA would therefore not have considered Villhauer and more importantly would not have expected that by using a "6-membered" ring as Uracil in the resulting DPP-IV compound would have resulted in a loss of potency.

VI. CONCLUSION

133. Claims 4 and 12 of the '689 Patent are invalid for obviousness-type double patenting over claim 162 of the Feng patent in view of Kim 1998 and the common knowledge of a POSA as set forth in the expert reports of Dr. David P. Rotella.

134. Claims 4 and 12 of the '689 Patent are invalid for obviousness under 35 U.S.C. § 103 over the prior art references set forth above and further expounded upon in Dr. Ferraris' opening and reply expert reports.

135. This Court should award Defendants costs.

VII. RESERVATION

136. The facts stated within are not exhaustive and are merely representative of the facts that Defendants may present evidence of at trial. Defendants reserve the right to present these and any such additional facts that are commensurate with their interrogatory responses, deposition testimony, expert reports, and any orders or requests of the Court, and/or are necessary to respond to the evidence presented by Plaintiffs at trial.

B. **Defendant intends to prove the following contested facts with regard to damages:**

Not applicable at this time. However, should Plaintiffs at any time make a request for an award of damages, compensatory or otherwise, Defendants reserve the right to contest any such claim, which may include submitting facts and other proof on the issue of damages or potential damages including the lack thereof of such damages.

TAB 8

8. PLAINTIFFS' CAUSES OF ACTION AND AFFIRMATIVE DEFENSES

A. Plaintiffs make the following causes of action.

Plaintiffs assert that the products described in Torrent's ANDA Nos. 21-0159, 21-0160, and 21-0161, and in Indoco's ANDA Nos. 210002 and 209998 would, if allowed on the market, infringe claims 4 and 12 of Takeda's '689 patent.[1] Accordingly, pursuant to 35 U.S.C. § 271(e)(4), Takeda seeks an order barring FDA from approving Defendants' ANDAs until after the '689 patent expires. Defendants have stipulated to infringement of claims 4 and 12 of the '689 patent.

B. To the extent there is a cross-claim, counterclaim or other claim for affirmative relief against the Plaintiffs, Plaintiffs raise the following affirmative defenses.

Defendants have withdrawn their counterclaims for non-infringement in this action.

Defendants assert counterclaims/affirmative defenses of invalidity for each asserted claim of the '689 patent, as set forth in the expert reports of their experts Drs. Dana Ferraris and David Rotella. Plaintiffs raise the affirmative defense that each of its asserted claims are valid over Defendants' cited prior art and expert testimony.

[1] Claims 4 and 12 of the '689 patent are the only claims that Plaintiffs are asserting against Defendants at trial. No other claims from the '689 patent will be asserted against Defendants at trial.

TAB 9

9. DEFENDANTS' CLAIMS AND AFFIRMATIVE DEFENSES

A. Defendants make the following affirmative defenses.

DEFENDANTS' CLAIMS AND AFFIRMATIVE DEFENSES

1. Defendants Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc. (collectively, "Torrent") together with Defendant Indoco Remedies Ltd. ("Indoco") seek a judgment declaring that the asserted claims, (i.e., claims 4 and 12), of the '689 patent are invalid under 35 U.S.C. §103(a) and/or the judicially-created doctrine of obviousness-type double patenting.

2. Defendants Torrent and Indoco seek a judgment declaring that Torrent and Indoco have a lawful right to obtain FDA approval for the drug products described in Torrent's and Indoco's Abbreviated New Drug Applications ("ANDAs"), and that Torrent and Indoco have a lawful right to manufacture, import, use, sell, and/or offer to sell such drug products in the United States (as described in such ANDAs).

3. Defendants Torrent and Indoco, along with the affirmative defense that claims 4 and 12 of the '689 patent are invalid under the judicially-created doctrine of obviousness-type double patenting and/or 35 U.S.C. §103(a), further contend as an affirmative defense that neither the filing of Torrent's and Indoco's ANDAs nor the defense of this action gives rise to or constitutes an exceptional case under 35 U.S.C. § 285.

4. Defendants Torrent and Indoco seek such other and further relief as the Court may deem just and proper, including but not limited to any costs and/or expenses.

B. To the extent Defendants have a cross-claim, counterclaim or other claim for affirmative relief, those claims are as follows.

Claims 4 and 12 of the '689 patent (i.e., the asserted claims) are invalid.[2] Defendants incorporate by reference Sections 1, 2, 3, 5, 7, 9.A, 11, 12.C, 16, and 18 and the exhibits referenced therein.

[2] Defendants contend that claims 4 and 12 of the '689 patent are invalid as obvious under 35 U.S.C. § 103 and the doctrine of obviousness-type double patenting, as set forth in the reports of their experts Dr. Ferraris and Dr. Rotella, respectfully. No other arguments for invalidity will be asserted at trial.

TAB 10

10. PLAINTIFFS' WITNESSES (Aside from those called for impeachment purposes, only the witnesses and rebuttal witnesses whose names and addresses are listed below will be permitted to testify at trial.)

A. On liability Plaintiffs intend to call the following witnesses who will testify in accordance with the following summaries. (For witnesses who have been deposed, a statement that the witness's testimony will be in conformity with his/her deposition testimony is sufficient. For witnesses who have not been deposed, please include a detailed narrative of the witness's testimony)

Pursuant to Fed. R. Civ. P. 26(a)(3), Plaintiffs submit that because infringement of all asserted claims has been stipulated by Defendants, Plaintiffs do not presently intend to call any witnesses on liability. Plaintiff reserves the right to call any witnesses on Defendants' witness lists and to supplement or amend Plaintiffs' witness list.

B. On damages Plaintiffs intend to call the following witnesses who will testify in accordance with the following summaries. (For witnesses who have been deposed, a statement that the witness's testimony will be in conformity with his/her deposition testimony is sufficient. For witnesses who have not been deposed, please include a detailed narrative of the witness's testimony)

Not applicable at this time. Plaintiffs do not at this time seek monetary damages. Instead, Plaintiffs request statutory relief as set forth in 35 U.S.C. § 271.

C. Defendants object to the following witnesses for the reasons stated:

Not applicable as Plaintiffs are intending to not call any fact witnesses in-person or by deposition to establish liability of Defendants.

TAB 11

11. DEFENDANTS' WITNESSES (Aside from those called for impeachment purposes, only the witnesses and rebuttal witnesses whose names and addresses are listed below will be permitted to testify at trial.)

A. On liability Defendants intend to call the following witnesses who will testify in accordance with the following summaries (For witnesses who have been deposed, a statement that the witness's testimony will be in conformity with his/her deposition testimony is sufficient. For witnesses who have not been deposed, please include a detailed narrative of the witness's testimony)

Pursuant to Fed. R. Civ. P. 26(a)(3), and the fact that no depositions were taken by either side during fact discovery, Defendants do not intend to call any fact witnesses on liability, either in-person or by deposition. Defendants reserve the right to call any witnesses on Plaintiffs' witness list and to supplement or amend Defendants witness list in response to any amendments or modifications made by Plaintiffs to their witness list.

B. On damages Defendants intend to call the following witnesses who will testify in accordance with the following summaries. (For witnesses who have been deposed, a statement that the witness's testimony will be in conformity with his/her deposition testimony is sufficient. For witnesses who have not been deposed, please include a detailed narrative of the witness's testimony)

Not applicable at this time as Plaintiffs are not asserting any claims for damages against Defendants.

C. Plaintiffs object to the following witnesses for the reasons stated:

Not applicable as Defendants are intending not to call any fact witnesses in-person or by deposition.

TAB 12

TAB 12A

12. EXPERT AND SPECIALIZED LAY OPINION WITNESSES (No expert or specialized lay opinion witness offering scientific, technical or other specialized knowledge will be permitted to testify at trial unless listed below. A summary of the expert qualifications and a copy of his/her report must be provided for the Court's review at the pretrial conference. No opposing counsel shall be permitted to question the expert's qualifications unless the basis of the objection is set forth herein.)

A. Plaintiffs' expert and specialized lay opinion witness is:

Dr. David E. Nichols, Ph.D. The subject matter of Dr. Nichols' proposed testimony is set forth in his expert reports, which have been served on the Defendants and copies of which were provided for the Court's review. Specifically, Dr. Nichols will testify in rebuttal to Defendants' experts' arguments on invalidity based on 35 U.S.C. § 103 and obviousness-type double patenting, which Defendants must prove by clear and convincing evidence. Consistent with his expert report, Dr. Nichols will testify that none of the prior art suggested by Defendants' experts, alone or in combination, would render the inventions disclosed in the asserted claims of the '689 patent obvious to a person of ordinary skill in the art ("POSA") under either 35 U.S.C. § 103 or the judicially-created doctrine of obviousness-type double patenting.

Dr. Nichols is a widely-published and recognized expert in pharmacology and medicinal chemistry who has spent the past half century working on drug discovery, in both academics and in industry. Dr. Nichols received a Ph.D. in Medicinal Chemistry from the University of Iowa in 1973, and a B.S. in Chemistry from the University of Cincinnati in 1969. Dr. Nichols also completed postdoctoral studies in Pharmacology at the University of Iowa where he was a Postdoctoral Fellow from 1973-1974. He is currently an Adjunct Professor at the University of North Carolina, Chapel Hill, Eshelman School of Pharmacy since 2012, is the Distinguished Professor Emeritus of Medicinal Chemistry and Molecular Pharmacology at Purdue University, and is an Adjunct Professor Emeritus of Pharmacology and Toxicology at Indiana University.

Dr. Nichols is also the Former Robert C. and Charlotte P. Anderson Distinguished Chair in Pharmacology at Purdue University. While at Purdue University, Dr. Nichols was a Professor of Pharmacology (between 1985-2012), a Professor of Medicinal Chemistry (between 1984-2012), an Associate Professor of Medicinal Chemistry (between 1979-1984) and an Assistant Professor of Medicinal Chemistry (between 1974-1979). Dr. Nichols was also an Adjunct Professor of Pharmacology and Toxicology at the Indiana University School of Medicine (between 2003-2012).

In the course of his career, Dr. Nichols has authored or co-authored over 285 peer-reviewed scientific journal publication articles, over 25 book chapters or monographs, over 15 symposium proceeding publications, and over 170 abstracts for presentations at professional national meetings. Dr. Nichols is an inventor or co-inventor on nine granted U.S. Patents, has been an invited speaker over 35 times at National or International Symposia, and given over 90 seminar presentations as an invited speaker. At trial, Plaintiffs will present Dr. Nichols' complete *curriculum vitae* to the Court.

Defendant Torrent argues in its portion of the present Joint Pretrial submission that Dr. Nichols somehow "admitted" that he is not qualified to offer opinion testimony on the subject matter of the '689 patent claims to be tried. That is not correct. To the contrary, Dr. Nichols' testified that a POSA does not require experience in the specific fields of DPP-IV inhibitors, diabetes, or type II diabetes. Dr. Nichols testified that a POSA requires skills and knowledge of medicinal chemistry "that are applicable to any field they got into." (Id. at 177:8-20, 179:3-11, 179:22-183:11, 183:19-184:22, 237:3-239:5, and 239:19-240:9.) In that regard, Defendants'

expert, Dr. Ferraris, expressly acknowledged that Dr. Nichols is "qualified as an expert to offer the opinions that he's given in the case." (See Ferraris Dep. Tr., 242:7-17.)

TAB 12B

B. Defendants' objections to the qualifications of Plaintiffs' experts and specialized lay opinion witnesses are:

As an initial matter, Defendant Torrent objects to the inclusion of Plaintiffs' argument in Section 12.A for why (in their opinion) Dr. Nichols is qualified to offer opinion testimony on the subject matter of the '689 patent. Section 12.A., as evidenced by the text of the header itself, limits a party such as Takeda here to only state (1) who they will be relying on as an expert witness in this action; (2) what are the expert's qualifications; and (3) what is the expected testimony of the expert. Therefore, any other details and/or arguments raised therein by Takeda should be ignored outright. Nevertheless, Defendant Torrent reserves the right to address Plaintiffs' improperly placed argument regarding the qualifications of Dr. Nichols at the pretrial conference and at trial.

Defendants object to Plaintiffs' expert's testimony to the extent Dr. Nichols' attempts to opine on matters outside the scope of his Rule 26(a)(2)(B) expert reports or deposition, anything outside of his experience or purported area of expertise, and to testimony objectionable under one or more of Fed. R. Evid. 401, 402, 403, 611, 702, and 703. Defendants further object to the extent that Dr. Nichols' attempts to opine or testify on legal issues that are beyond his experience and knowledge. Defendants reserve all rights to conduct any necessary *voir dire* of Dr. Nichols' expert qualifications and opinions at trial.

Defendant Torrent further objects to any testimony by Dr. Nichols on the issue of the validity of the '689 patent, and the asserted claims therein, on the ground that Dr. Nichols admitted at his deposition that to offer an opinion for the purposes of this action on the issue of validity of the claims at issue in the '689 patent a person of ordinary skill in the art must have at least several years of relevant practical, academic, or industrial experience researching or

developing drugs for treating type 2 diabetes, which Dr. Nichols admits he does not possess. Defendant Torrent additionally objects to any testimony by Dr. Nichols on the issue of the validity of the claims at issue of the '689 patent on the further ground that Dr. Nichols admitted that he is not an expert in diabetes—which is the subject matter of the '689 patent.

Defendant Indoco does not at this time join in Torrent's objection to Dr. Nichols' testimony based on his lack of experience in type II diabetes and its research. Instead, Indoco reserves all rights at trial to address Dr. Nichols' admitted failure to have experience in researching and developing DPP-IV inhibitors or in type II diabetes research and drug development.

TAB 12C

C. Defendants' expert and specialized lay opinion witnesses are:

David P. Rotella, Ph.D. (for both Torrent and Indoco)

Dr. Rotella is currently the Margaret and Herman Sokol Professor of Chemistry in the Department of Chemistry and Biochemistry and in the Sokol Institute of Pharmaceutical Life Sciences at Montclair State University. Dr. Rotella has been a Professor of Chemistry at Montclair State University since 2011. Dr. Rotella is also currently an adjunct professor in the Department of Pharmaceutical Sciences at the University of Pittsburg (since 2010), in the Center of Drug Discovery at Northeastern University (since 2010), and in the Department of Medicinal Chemistry at the University of Mississippi (since 2009).

Dr. Rotella received a Ph.D. in Medicinal Chemistry from the Ohio State University in 1985 and a B.S. Pharm. from the University of Pittsburgh in 1981. Dr. Rotella completed his postdoctorate studies at The Pennsylvania State University where he was a Postdoctoral Scholar from 1985-1987.

Prior to Dr. Rotella's university professorships, he was a research scientist at multiple pharmaceutical companies including at Bristol-Myers Squibb PRI, Lexicon Pharmaceuticals, and Wyeth Research/Pfizer from 1991-2010. While a researcher in industry, Dr. Rotella focused his industry experience on drug discovery and development regarding several types of novel inhibitors, including DPP-IV inhibitors and PDE5 inhibitors.

Dr. Rotella has co-authored more than 20 abstracts for the presentation at professional meetings, over 40 peer-reviewed journal articles, and seven book chapters, including publications in the areas of DPP-IV inhibitors and treatment of Type 2 diabetes. Dr. Rotella has

also received numerous honors, fellowships and awards, and is an inventor or co-inventor on seven granted patents.

The subject matter of Dr. Rotella's proposed testimony is set forth in his expert reports, which have been served on Plaintiffs and copies of which will be provided for the Court's review, including his complete *curriculum vitae*, at the pretrial conference on October 2, 2019. Consistent with his expert reports, Dr. Rotella will testify that claims 4 and 12 of the '689 patent are invalid for obviousness-type double patenting over claim 162 of U.S. Patent No. 7,723,444 (the "Feng patent") in view of Kim et al., "Anti-diabetic activity of Constituents of Lycii Fructus," The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("Kim 1998") and the common knowledge of a POSA as set forth in the expert reports of Dr. David P. Rotella. . At trial, Defendants will present Dr. Rotella's complete *curriculum vitae* to the Court.

A summary of Dr. Rotella's expert qualifications and a copy of his reports, including his curriculum vitae, will be provided for the Court's review at the pretrial conference on October 2, 2019.

Dana Ferraris, Ph.D. (for both Torrent and Indoco)

Dr. Ferraris is currently the Chair of the Department of Chemistry at McDaniel College. Since 2015 he has been a member of the faculty of the Department of Chemistry at McDaniel College. He was formerly a visiting professor of Chemistry at Stevenson University.

Dr. Ferraris received his B.A. in Biochemistry from the Lafayette College in 1994, a Ph.D. in Organic Chemistry from Johns Hopkins University in 2000, and a MBA from Carey Business School of Johns Hopkins University in 2009.

From 1999-2004, Dr. Ferraris worked as a senior scientist and principal scientist on drug discovery projects at various pharmaceutical companies, including Guilford Pharmaceuticals, MGI Pharma, and Eisai Pharmaceuticals. From 2009-2014, Dr. Ferraris worked as a principal scientist at John Hopkins University Brain Science Institute Neurotranslational Drug Discovery Program.

Dr. Ferraris is currently the President of the Maryland Section of the American Chemical Society ("ACS"). He has been a member of ACS since 1994, in which time he have held various positions in the organization, including Associate Member of the Budget and Finance Committee, Member of the Committee on Economic and Professional Affairs, and Councilor of the Maryland Section.

Dr. Ferraris has authored and co-authored more than 50 peer reviewed articles the majority of which are directly related to medicinal chemistry projects in which he was an active member. Dr. Ferraris has published multiple pieces on DPP-IV inhibitors. He has received several awards and honors including the Ernest M. Marks Award for excellence in chemical research at Johns Hopkins University, and Ira G. Zepp Teaching Enhancement Grant. Dr. Ferraris is a co-inventor on several United States patents.

The subject matter of Dr. Ferraris' proposed testimony is set forth in his expert reports, which have been served on Plaintiffs and copies of which will be provided for the Court's review, including his complete *curriculum vitae*, at the pretrial conference on October 2, 2019. Consistent with his reports, Dr. Ferraris will testify that claims 4 and 12 of the '689 patent are invalid for obviousness under 35 U.S.C. § 103(a) in view of the prior art and the common

knowledge of a POSA. At trial, Defendants will present Dr. Ferraris' complete *curriculum vitae* to the Court.

TAB 12D

D. Plaintiffs' objections to the qualifications of Plaintiffs' experts and specialized lay opinion witnesses are:

Plaintiffs object to Defendants' experts' testimony to the extent they attempt to opine on matters outside the scope of their Rule 26(a)(2)(B) expert reports or deposition, anything outside of their experience or purported area of expertise, and to testimony objectionable under one or more of Fed. R. Evid. 401, 402, 403, 611, 702, and 703. Plaintiffs further object to the extent that Defendants' experts' attempts to opine or testify on legal issues that are beyond their experience and knowledge. Further, Plaintiffs object to the opinions of Drs. Ferraris and Rotella because both have engaged in a hindsight-based analysis that is impermissible under controlling law. Plaintiffs reserve all rights to conduct any necessary *voir dire* of Defendants' experts' qualifications and opinions at trial.

TAB 13

13. PLAINTIFFS' DEPOSITIONS (List, by page and line, all deposition testimony to be offered into evidence. All irrelevant and redundant matters and all colloquy between counsel must be eliminated, unless ruled relevant. Deposition testimony to be used solely for impeachment purposes need not be listed).

Not applicable. Plaintiffs, subject to any of the Court's rulings on admissibility, intend to introduce only the live testimony of Dr. Nichols and to use deposition testimony from Dr. Rotella and Dr. Ferraris only for impeachment purposes. Should something unforeseen occur that makes such live testimony impossible (such as the death or incapacity of a witness), the parties will agree to exchange designations as soon as possible after being informed of such event.

TAB 14

14. DEFENDANTS' DEPOSITIONS (List, by page and line, all deposition testimony to be offered into evidence. All irrelevant and redundant matters and all colloquy between counsel must be eliminated, unless ruled relevant. Deposition testimony to be used solely for impeachment purposes need not be listed).

Not applicable. Defendants, subject to any of the Court's rulings on admissibility, intend to introduce only the live testimony of Dr. Rotella and Dr. Ferraris and to use deposition testimony from Dr. Nichols only for impeachment purposes. Should something unforeseen occur that makes such live testimony impossible (such as the death or incapacity of an expert witness), the parties will agree to exchange deposition designations as soon as possible after being informed of such event.

TAB 15

15. PLAINTIFFS' EXHIBITS (Except for exhibits the need for which could not reasonably have been foreseen or which are used solely for impeachment purposes, only the exhibits set forth on the exhibit list attached hereto may be introduced at trial. Any objection to an exhibit, and the reason for said objection, must be set forth below or it shall be deemed waived. All parties hereby agree that it will not be necessary to bring in the custodian of any exhibit as to which no such objection is made.)

A. Plaintiffs intend to introduce into evidence the exhibits listed on the attached exhibit list (list by number with a description of each exhibit).

Plaintiffs' exhibit list is attached hereto. Plaintiffs' Trial Exhibit List is preliminary in nature and subject to revision. Plaintiffs expressly reserve the right to modify, supplement, or amend these trial exhibits as a result of, for example, following substantive review of Defendants' trial exhibits, resolution of pending issues or motions, further discovery, documents produced pursuant to L. Pat. R. 3.6(j)(2), reductions in claims and defenses by the parties to streamline the case for trial, a decision on any motion by the Court, and the pre-trial and trial meet and confer process. Furthermore, the inclusion of any trial exhibit on Plaintiffs' Trial Exhibit List does not mean that Plaintiffs concede that such trial exhibit is admissible.

For each exhibit, Plaintiffs reserve the right to rely on, use and move into evidence (1) any native or color version, (2) any metadata, (3) excerpts (rather than the entire exhibits), and (4) a summary, chart, or calculation, e.g., under Fed. R. Evid. 1006.

In addition to the documents listed in Plaintiffs' Trial Exhibit List, Plaintiffs reserve the right to present their case by introducing exhibits presented, submitted, and introduced by Defendants in this action. Plaintiffs also reserve the right to offer exhibits not set forth in their exhibit list for purposes of impeachment and/or cross-examination. Plaintiffs' exhibits will be identified with PTX numbers.

B. Defendants object to the introduction of plaintiffs' exhibits (set forth number of an exhibit and grounds for objection):

Please see **Tab 15** annexed hereto.

In addition to Defendants' objections included in Plaintiffs' Trial Exhibit List, Defendants reserve the right to supplement, amend, revise, or otherwise modify or add to their objections in light of any rulings on any pending or later raised motions, or other rulings of the Court. Defendants reserve the right to use any exhibit on Plaintiffs' Trial Exhibit List, and regardless of whether such exhibit appears on Defendants' Trial Exhibit List. Defendants further reserve the right to use any document or thing for rebuttal or impeachment purposes regardless of whether found in this list.

Defendants object to Plaintiffs offering as evidence exhibits related to Defendants' ANDAs or infringement in general as such evidence is not relevant to any claims or defenses currently in the case.

DEFENDANTS' KEY TO OBJECTIONS TO PLAINTIFFS TRIAL EXHIBIT LIST

Code	Objection
AU	Authenticity or Identification (FRE 901)
B	Violates Best Evidence Rule (FRE 1002-1004)
D	Duplicative/Cumulative
DE	Demonstrative/Should Not Be Admitted Into Evidence
F	Foundation (FRE 901)
H	Hearsay (FRE 801-802)
HC	Highly Confidential – Requires Sealed Courtroom for Introduction
ID	Improper description
IL	Illegible
IN	Incomplete (FRE 106)
IS	Improper Summary of Voluminous Records (FRE 1006)
M	Entry includes multiple documents
MD	Mischaracterizing or Misleading Description of Underlying Document
N	Never Produced/Provided
O	Offer for Compromise/Settlement (FRE 408)
P	Prejudice/Confusion/Waste of Time/Misleading (FRE 403)
PR	Privilege/Work Product
R	Relevance (FRE 401-402)

Takeda Pharma et al. v. Torrent Pharma et al., C.A. No. 17-3186 (consolidated)
Plaintiffs' Trial Exhibit List

Trial Exhibit Number	Doc Date	Document Description	Beg Bates	End Bates	Defendants' Objections
PTX-0001	9/8/2019	Orange Book Listing for NESINA®, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022271&Appl_type=N	TAK-ALOG_00413810	TAK-ALOG_00413812	AU, R, H, F
PTX-0002	9/8/2019	Orange Book Listing for KAZANO®, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=203414&Appl_type=N	TAK-ALOG_00413813	TAK-ALOG_00413815	AU, R, H, F
PTX-0003	9/8/2019	Orange Book Listing for OSENI®, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=004&Appl_No=022426&Appl_type=N	TAK-ALOG_00413816	TAK-ALOG_00413818	AU, R, H, F
PTX-0004	6/2019	Highlights of Prescribing Information – NESINA (alogliptin) tablets. Initial U.S. Approval: 2013, label revised June 2019	TAK-ALOG_00413819	TAK-ALOG_00413849	AU, P, R, H, F
PTX-0005	6/2019	Highlights of Prescribing Information – KAZANO (alogliptin and metformin HCL) tablets, for oral use. Initial U.S. Approval: 2013, label revised June 2019	TAK-ALOG_00413850	TAK-ALOG_00413884	AU, P, R, H, F

Trial Exhibit Number	Doc Date	Document Description	Beg Bates	End Bates	Defendants' Objections
PTX-0006	6/2019	Highlights of Prescribing Information – OSENI (alogliptin and pioglitazone) tablets. Initial U.S. Approval: 2013, label revised June 2019	TAK-ALOG_00413885	TAK-ALOG_00413929	AU, P, R, H, F
PTX-0007	1/25/2013	NESINA® NDA Approval Letter (NDA No. 022271) from FDA, dated January 25, 2013	TAK-ALOG_00413930	TAK-ALOG_00413937	AU, P, R, H, F
PTX-0008	1/25/2013	KAZANO® NDA Approval Letter (NDA No. 203414) from FDA, dated January 25, 2013	TAK-ALOG_00413938	TAK-ALOG_00413944	AU, P, R, H, F
PTX-0009	1/25/2013	OSENI® NDA Approval Letter (NDA No. 022426) from FDA, dated January 25, 2013	TAK-ALOG_00413945	TAK-ALOG_00413951	AU, P, R, H, F
PTX-0010	12/2004	Richard B. Silverman, "The Organic Chemistry of Drug Design and Drug Action," 7-120 (2d ed. 2004)	TAK-ALOG_00413952	TAK-ALOG_00414072	AU, F, H, P, R

Trial Exhibit Number	Doc Date	Document Description	Beg Bates	End Bates	Defendants' Objections
PTX-0011	6/4/2015	Mylan Pharmaceuticals, Inc. v. Astrazeneca - Declaration of David P. Rotella, Ph.D.	TAK-ALOG_00414108	TAK-ALOG_00414211	H, F, R
PTX-0012	9/16/2019	David Rotella Handwritten Notes 1 (Rotella Dep. Ex. 10)	N/A	N/A	R, H, F, P, ID
PTX-0013	9/16/2019	David Rotella Handwritten Notes 2 (Rotella Dep. Ex. 11)	N/A	N/A	R, H, F, P, ID
PTX-0014	9/16/2019	David Rotella Handwritten Notes 3 (Rotella Dep. Ex. 13)	N/A	N/A	R, H, F, P, ID

TAB 16

16. DEFENDANTS' EXHIBITS (Except for exhibits the need for which could not reasonably have been foreseen or which are used solely for impeachment purposes, only the exhibits set forth on the exhibit list attached hereto may be introduced at trial. Any objection to an exhibit, and the reason for said objection, must be set forth below or it shall be deemed waived. All parties hereby agree that it will not be necessary to bring in the custodian of any exhibit as to which no such objection is made).

A. Defendants intend to introduce into evidence the exhibits listed on the attached exhibit list.

Defendants' Trial Exhibit List is preliminary in nature and subject to revision. Defendants expressly reserve the right to modify, supplement, or amend these trial exhibits as a result of, for example, following substantive review of Plaintiffs' trial exhibits, resolution of pending issues or motions, further discovery, documents produced pursuant to L. Pat. R. 3.6(j)(2), reductions in claims and defenses by the parties to streamline the case for trial, a decision on any motion by the Court, and the pre-trial and trial meet and confer process. Furthermore, the inclusion of any trial exhibit on Defendants' Trial Exhibit List does not mean that Defendants concede that such trial exhibit is admissible.

For each exhibit, Defendants reserve the right to rely on, use and move into evidence (1) any native or color version, (2) any metadata, (3) excerpts (rather than the entire exhibits), and (4) a summary, chart, or calculation, e.g., under Fed. R. Evid. 1006.

In addition to the documents listed in Defendants' Trial Exhibit List, Defendants reserve the right to present their case by introducing exhibits presented, submitted, and introduced by Plaintiffs in this action. Defendants also reserve the right to offer exhibits not set forth in their exhibit list for purposes of impeachment and/or cross-examination. Defendants exhibits will be identified with DTX numbers.

B. Plaintiffs object to the introduction of defendants' exhibits (set forth number of an exhibit and grounds for objection):

Please see **Tab 16** annexed hereto.

In addition to Plaintiffs' objections included in Defendants' Trial Exhibit List, Plaintiffs reserve the right to supplement, amend, revise, or otherwise modify or add to their objections in light of any rulings on any pending or later raised motions, or other rulings of the Court. Plaintiffs reserve the right to use any exhibit on Defendants' Trial Exhibit List, and regardless of whether such exhibit appears on Plaintiffs' Trial Exhibit List. Plaintiffs further reserve the right to use any document or thing for rebuttal or impeachment purposes regardless of whether found in this list.

PLAINTIFFS' KEY TO OBJECTIONS TO DEFENDANTS' TRIAL EXHIBIT LIST

Code	Objection
A	Authenticity or Identification (FRE 901)
F	Foundation (FRE 901)
H	Hearsay (FRE 801-802)
R	Relevance or Prejudicial (FRE 401-403)

Takeda Pharma et al. v. Torrent Pharma et al., C.A. No. 17-3186 (consolidated)
Proposed Pretrial Order
Defendants' Trial Exhibit List

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
DTX-0001	Nichols Exhibit 1; Rotella Exhibit 4	N/A	N/A	7/19/2019	Rebuttal Expert Report of Dr. David E. Nichols, Ph.D. on Validity of U.S. Patent Nos. 7,807,689, 8,288,539, and 8,173,663 dated July 19, 2019 and all exhibits and references cited therein.	H, R
DTX-0002	N/A	N/A	N/A	3/5/2018	Indoco's March 5, 2018 Invalidity Contentions	H, R, F
DTX-0003	N/A	N/A	N/A	4/16/2018	Plaintiffs' April 16, 2018 Responses To Indoco's Invalidity Contentions	H, R, F
DTX-0004	Nichols Exhibit 12	N/A	N/A	9/11/2019	Defendants' Notice of Deposition of Dr. David E. Nichols	H, R, F
DTX-0005	Nichols Exhibit 8; Rotella Exhibit 1	N/A	N/A	6/7/2019	Opening Expert Report of David P. Rotella, Ph.D. Regarding the Invalidity of U.S. Patent No. 7,807,689	H, R
DTX-0006	Nichols Exhibit 13; Ferraris Exhibit 2; Rotella Exhibit 6	N/A	N/A	6/14/2019	Opening Expert Report of Dana Ferraris, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689, 8,288,539 and 8,173,633	H, R
DTX-0007	Nichols Exhibit 14; Ferraris Exhibit 3; Rotella Exhibit 16	N/A	N/A	8/23/2019	Reply Expert Report of Dana Ferraris, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689, 8,288,539 and 8,173,633	H, R
DTX-0008	N/A	N/A	N/A	9/12/2017	Takeda's Initial Disclosures Pursuant to Fed. R. Civ. P. 26(a)(1)(A)	H, R, F
DTX-0009	N/A	N/A	N/A	9/12/2017	Defendant's Torrent Pharmaceuticals Ltd. and Torrent Pharma, Inc.'s Initial Disclosures Pursuant to Fed.	H, R, F

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
					R. Civ. P. 26(a)(1)	
DTX-0010	N/A	N/A	N/A	10/6/2017	Defendant's Torrent Pharmaceuticals Ltd. and Torrent Pharma, Inc.'s First Set of Request for Production of Documents (Nos. 1-93) to Plaintiffs	H, R, F
DTX-0011	N/A	N/A	N/A	11/17/2017	Plaintiff's First Set of Requests for the Production of Documents and Things (Nos. 1-49)	H, R, F
DTX-0012	N/A	N/A	N/A	11/20/2017	Takeda's Objections and Responses to Defendants' First Set for Requests for the Productions of Documents (Nos. 1-93)	H, R, F
DTX-0013	N/A	N/A	N/A	12/18/2017	Defendant's Torrent Pharmaceuticals Ltd. and Torrent Pharma, Inc.'s Responses to Plaintiff's First Set of Requests for the Production of Documents and Things (Nos. 1-49)	H, R, F
DTX-0014	N/A	N/A	N/A	10/6/2017	Defendant's Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc.'s First Set of Interrogatories to Plaintiffs (Nos. 1-10)	H, R, F
DTX-0015	N/A	N/A	N/A	11/17/2017	Plaintiffs' First Set of Interrogatories (Nos. 1-9) to Defendants	H, R, F
DTX-0016	N/A	N/A	N/A	11/20/2017	Takeda's Objections and Responses to Defendants' First Set of Interrogatories (Nos. 1-10)	H, R, F
DTX-0017	N/A	N/A	N/A	12/18/2017	Defendants' Responses to Plaintiffs' First Set of Interrogatories (Nos. 1-9)	H, R, F

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
DTX-0018	N/A	N/A	N/A	8/27/2019	Takeda's Supplemental Objections and Responses to Defendants' First Set of Interrogatories (Nos. 1-10)	H, R, F
DTX-0019	N/A	N/A	N/A	9/27/2018	Defendants Torrent Pharmaceuticals Ltd. and Torrent Pharma, Inc.'s Second Set of Interrogatories to Plaintiffs (Nos. 11-14)	H, R, F
DTX-0020	N/A	N/A	N/A	10/25/2017	Defendants Torrent Pharmaceuticals Limited and Torrent Pharma, Inc.'s Initial Invalidity Contentions for U.S. Patent Nos. 7,807,689, 8,173,663, 8,288,539 and 8,900, 638	H, R, F
DTX-0021	N/A	N/A	N/A	12/11/2017	Plaintiffs' December 11, 2017 Responses To Torrent's Invalidity Contentions	H, R, F
DTX-0022	N/A	N/A	N/A	7/12/2019	Plaintiffs' Initial Infringement Contentions for U.S. Patent Nos. 9,125,910 and 9,278,096 Against Torrent Pharmaceuticals Limited and Torrent Pharma Inc.	H, R, F
DTX-0023	N/A	TOR-NESINA-00142888	TOR-NESINA-00142894		Assignment Data for U.S. Patent 7,723,344	H, R, F
DTX-0024	N/A	N/A	N/A	1/29/2018	Defendant, Indoco Remedies LTD.'s Rule 26(a)(1) Initial Disclosures (Case No.: 2:17-cv-7301-SRC-CLW)	H, R, F
DTX-0025	N/A	N/A	N/A	1/29/2018	Defendant, Indoco Remedies LTD.'s Rule 26(a)(1) Initial Disclosures (Case No.: 2:18-cv-55-SRC-CLW)	H, R, F

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
DTX-0026	N/A	N/A	N/A	1/29/2018	Takeda's Initial Disclosures Pursuant to Fed. R. Civ. P. 26(a)(1)(A) (Civil Action Nos. 17-7301 and 18-55)	H, R, F
DTX-0027	N/A	N/A	N/A	7/24/2018	Plaintiffs' First Set of Requests for the Production of Documents and Things (Nos. 1-49)	H, R, F
DTX-0028	N/A	N/A	N/A	7/24/2018	Plaintiffs' First Set of Interrogatories (No. 1-9) to Defendant	H, R, F
DTX-0029	N/A	N/A	N/A	8/30/2018	Defendant Indoco Remedies LTD.'s Objections and Responses to Plaintiffs' First Set of Requests the Production of Documents and Things (Nos. 1-49)	H, R, F
DTX-0030	N/A	N/A	N/A	8/30/2018	Defendant Indoco Remedies LTD.'s Objections and Responses to Plaintiffs' First Set of Interrogatories (Nos. 1-9) to Defendant	H, R, F
DTX-0031	N/A	N/A	N/A	8/31/2018	Defendant Indoco Remedies LTD.'s First Set of Requests For Production of Documents and Things	H, R, F
DTX-0032	N/A	N/A	N/A	8/31/2018	Defendant Indoco Remedies LTD.'s First Set of Interrogatories to Plaintiffs	H, R, F
DTX-0033	N/A	N/A	N/A	10/5/2018	Takeda's Objections and Responses to Defendant's First Set of Requests for Production of Documents and Things	H, R, F
DTX-0034	N/A	N/A	N/A	10/5/2018	Takeda's Objections and Responses to Defendant's First St of	H, R, F

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
					Interrogatories to Plaintiffs	
DTX-0035	N/A	N/A	N/A	8/27/2019	Takeda's Supplemental Objections and Responses to Defendant's First St of Interrogatories to Plaintiffs	H, R, F
DTX-0036	N/A	N/A	N/A	9/9/2018	Defendant Indoco Remedies LTD.'s Supplemental Objections and Responses to Plaintiffs' First Set of Interrogatories (Nos. 1-9) to Defendant	H, R, F
DTX-0037	N/A	N/A	N/A	3/5/2018	Defendant Indoco Remedies LTD. Invalidity Contentions	H, R, F
DTX-0038	N/A	N/A	N/A	1/29/2018	Plaintiffs' Disclosure of Asserted Claims	H, R, F
DTX-0039	N/A	N/A	N/A	4/16/2018	Plaintiffs' Responses to Indoco's Invalidity Contentions	H, R, F
DTX-0040	Rotella Exhibit 3	N/A	N/A	8/23/2919	Reply Expert Report of David P. Rotella, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689	H, R
DTX-0041	N/A	N/A	N/A	9/16/2019	Defendants Torrent Pharmaceuticals Limited and Torrent Pharma, Inc.'s Supplemental Objections and Responses to Plaintiff's' First Set of Interrogatories (Nos. 1-9)	H, R, F
DTX-0042	N/A	N/A	N/A	06/14/2019	Opening Expert Report of Dr. David Nichols on Infringement of U.S. Patent Nos. 7,807,689, 8,288,539, and 8,173,663	H, R

Trial Exhibit Number	Deposition Exhibit No.	Defendants Tr Beg Bates	Defendants Tr End Bates	Doc Date	Description	Plaintiffs' Objections
DTX-0043	Nichols Exhibit 17	IndAlo0079514	IndAlo0079927	2/24/2012	Lupin Limited v. Takeda Pharmaceutical Company Limited - Reply Statement of the Patentee Under Rule 58	H, R, F, A
DTX-0044	Nichols Exhibit 18	IndAlo0079928	IndAlo0080130	6/4/2014	Letter to Sh. D.K. Rahut Controller of Patents and Designs enclosing Original Affidavit of Prof. David Earl Nichols along with enclosures	H, R, F
DTX-0045	Rotella Exhibit 14	TAK-ALOG00414108	TAK-ALOG00414211	6/4/2015	Mylan Pharmaceuticals, Inc. v. Astrazeneca - Declaration of David P. Rotella, Ph.D	H, R

TAB 17

17. JOINT EXHIBITS

1. The list of joint exhibits, which are pre-admitted in advance of trial, is attached hereto. The parties stipulate to the admissibility of these exhibits. The joint exhibits will be identified with JTX numbers.

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0001	Ferraris Exhibit 4; Rotella Exhibit 5	TAK-ALOG_00413714	TAK-ALOG_00413768	7/14/2017	U.S. Patent No. 7,807,689	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols; Deposition of Dana Ferraris; Deposition of David Rotella
JTX-0002	N/A	TAK-ALOG_00156012	TAK-ALOG_00186127	3/15/2005	File History of U.S. Patent No. 7,807,689 & References	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris
JTX-0003	Rotella Exhibit 8	TOR-NESINA 00127019	TOR-NESINA 00127088	5/25/2010	U.S. Patent No. 7,723,344	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Rebuttal Expert Report of David Nichols; Deposition of David Rotella
JTX-0004	N/A	TOR-NESINA 00142001	TOR-NESINA 00143216	5/25/2010	File History of U.S. Patent No. 7,723,344	David Rotella Opening Expert Report; David Rotella Reply Expert Report
JTX-0005	Nichols Exhibit 16; Ferraris Exhibit 8	IndAlo0000738	IndAlo0000839	1/16/2003	Kanstrup *et al.*, WO 03/004496 "DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Deposition of David Nichols; Deposition of Dana Ferraris

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0006	N/A	IndAlo0000840	IndAlo0000848	6/1/2002	Evans, Michael D., "Dipeptidyl peptidase IV inhibitors" IDrugs 2002 5(6):577-585	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0007	N/A	IndAlo0079503	IndAlo79513	9/1/2003	Anderson, Amy C. "The Process of Structure-Based Drug Design" Chemistry & Biology, Vol. 10, 787-797 (September 2003)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0008	N/A	TOR-NESINA 00126996; IndAlo0079175	TOR-NESINA 00127002; IndAlo0079181	6/19/1998	McGaughey, Georgia B., et al., "π-Stacking Interactions," The Journal of Biological Chemistry, Vol. 273, No. 25, Issue of June 19, pp. 15458–15463 (1998)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0009	Nichols Exhibit 5; Ferraris Exhibit 9; Rotella Exhibit 17	TOR-NESINA 00127789; IndAlo0079118	TOR-NESINA00127796; IndAlo0079125	2004	Bohm et al., "Scaffold hopping," Drug Discovery Today: Technologies 2004, Vol. 1, No. 3, 217-223 (December 2004)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols; Deposition of David Nichols; Deposition of Dana Ferraris; Deposition of David Rotella

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0010	Nichols Exhibit 10	TOR-NESINA 00126326; IndAlo0000952	TOR-NESINA 00126335; IndAlo0000963	2004	Aertgeerts, K., et al., "Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formulation", 13(2) PROTEIN SCI. 412-421 (Feb. 2004)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols; Deposition of David Nichols
JTX-0011	N/A	IndAlo0000946	IndAlo0000951	4/29/2003	Engel, M., et al., "The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism", 100(9) PNAS 5063-5068 (Apr. 29. 2003)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0012	N/A	IndAlo0000858	IndAlo0000945	2003	Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV", 40(3) Crit. Rev. Clin. Lab. Sci. 209-294 (2003)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0013	Nichols Exhibt 6; Ferraris Exhibit 5; Rotella Exhibit 7	IndAlo0000849	InAlo0000945	2003	Wiedeman, P.E. & Trevillyan, J.M., "Dipeptidyl peptidase IV inhibitors for the treatment of impaired glucose tolerance and type 2 diabetes", 4(4) Current Opinion in Investigational Drugs 412-420 (Apr. 2003)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols; Deposition of David Nichols; Deposition of David

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
						Rotella; Deposition of Dana Ferraris
JTX-0014	Ferraris Exhibit 7; Rotella Exhibit 18	TOR-NESINA 00127532; IndAlo0045116	TOR-NESINA 00127751; IndAlo0045335	3/4/2004	C.A. Patent No. 2,496,249 to Mark et al., entitled "8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments," published on March 4, 2004 ("Mark 2004")	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols; Deposition of Dana Ferraris; Deposition of David Rotella
JTX-0015	Nichols Exhibit 15; Ferraris Exhibit 6; Rotella Exhibit 9	InAlo0000374	InAlo0000737	1/16/2003	C.A. Patent No. 2,435,730 to Lotz et al., entitled "xanthines derivatives, the production thereof and their use as pharmaceutical compositions," published on September 6, 2002 ("CA '730")	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Deposition of David Nichols; Deposition of Dana Ferraris; Deposition of David Rotella
JTX-0016	Nichols Exhibit 9; Rotella Exhibit 12	TOR-NESINA 00126805	TOR-NESINA 00126810	7/3/1998	Kim et al., "Anti-diabetic Activity of Constituents of Lycii Fructus," The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("Kim 1998")	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Rebuttal Expert Report of David Nichols; Deposition of David Nichols; Deposition of David Rotella

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0017	N/A	TOR-NESINA 00126607	TOR-NESINA 00126621	4/1/1981	S. Parodi, *et al.*, "DNA-damaging Activity In Vivo and Bacterial Mutagenicity of Sixteen Hydrazine Derivatives as Related Quantitatively to their Carcinogenicity," Cancer Research 41, 1469–1482, April 1981	David Rotella Opening Expert Report; David Rotella Reply Expert Report
JTX-0018	N/A	TOR-NESINA 00126976	TOR-NESINA 00126995	5/23/1996	Lal et al., "Electrophilic NF Fluorinating Agents," Chemical Reviews, 1996, Vol. 96, No. 5, pp. 1737-1755	David Rotella Opening Expert Report; David Rotella Reply Expert Report
JTX-0019	N/A	TOR-NESINA 00127344; IndAlo0044978	TOR-NESINA 00127364; IndAlo0044996	1977	Berge et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66, pp. 1-19 (1977)	David Rotella Opening Expert Report; David Rotella Reply Expert Report; Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0020	Rotella Exhibit 15	TOR-NESINA 00143230	TOR-NESINA 00143565	2/5/2004	Hiramatsu, H. et al., WO 2004/011640 A1 entitled "Three-Dimensional Structure of Dipeptidyl Peptidase IV", published February 5, 2004	David Rotella Reply Expert Report; Deposition of David Rotella
JTX-0021	N/A	TOR-NESINA 00143225	TOR-NESINA 00143229	1998	Lin, Jian & John Welch et al., "Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics" Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 14020-14024 (1998)	David Rotella Reply Expert Report

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0022	N/A	TOR-NESINA 00143217	TOR-NESINA 00143224		Berger, Joel P. et al., "A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice" Endocrinol Diab Metab. 2018; 1:e2. https://doi.org/10.1002/edm2.2	David Rotella Reply Expert Report
JTX-0023	Nichols Exhibt 4	TOR-NESINA 00127003	TOR-NESINA 0012718	2011	Zhang, Zhiyuan et al., "Design and Synthesis of Pyrimidinone and Pyrimidinedione Inhibitors of Dipeptidyl Peptidase IV", 54 J. Med. Chem. 510-524 (2011)	David Rotella Reply Expert Report; Rebuttal Expert Report of David Nichols; Deposition of David Nichols
JTX-0024	N/A	TOR-NESINA 00126386	TOR-NESINA 00126391	2014	Sinha, Birandra et al., "Biotransformation of Hydrazine Derivatives in the Mechanism of Toxicity", 5(2) J. Drug Metabolism & Toxicity 1-6 (2014) ("Sinha"	David Rotella Reply Expert Report; Rebuttal Expert Report of David Nichols
JTX-0025	N/A	N/A	N/A	10/16/2012	U.S. Patent No. 8,288,539	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0026	N/A	N/A	N/A	41037.00	U.S. Patent No. 8,173,663	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0027	N/A	N/A	N/A		File History of Patent No. 8,288,539 & References	Opening Expert Report of Dana Ferraris; Reply Expert

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
						Report of Dana Ferraris
JTX-0028	N/A	N/A	N/A		File History of Patent No. 8,176,663 & References	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0029	N/A	IndAlo0000990	IndAlo0000996	8/25/1992	U.S. Patent No. 5,142,051 to Holy et al., N-Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity, issued Aug. 25, 1992	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0030	N/A	IndAlo0000997	IndAlo0001036	7/14/1998	U.S. Patent No. 5,780,476 to Underiner et al., Hydroxyl-Containing Xanthine Compounds, issued July 14, 1998	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0031	N/A	IndAlo0079268	IndAlo0079290	3/2/2004	U.S. Patent No. 6,699,871 to Edmondson et al., Beta-Amino Heterocyclic Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes, issued March 2, 2004	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0032	N/A	IndAlo0079291	IndAlo0079359	1/16/2003	International Publication WO 2003/004498 to Edmonson, Beta-amino Tetrahydroimidazo (1, 2-a) Pyrazines And Tetrahydrotrioazolo (4, 3-a) Pyrazines As Dipeptidyl Peptidase Inhibitors For The Treatment Or Prevention Of Diabetes, published Jan. 16, 2003	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris

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JTX-0033	N/A	IndAlo0000001	IndAlo0000373	9/6/2002	International Publication WO 2002/068420 A1, Xanthine Derivatives, Production and Use Thereof As Medicament, filed Feb. 21, 2002 and published Sept. 6, 2002	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0034	N/A	IndAlo0079111	IndAlo0079117	2002	Ahrén, B. et al., Inhibition Of Dipeptidyl Peptidase IV Improves Metabolic Control Over A 4-Week Study Period In Type 2 Diabetes, 25(5) Diabetes Care 869–875 (May 2002)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0035	N/A	IndAlo0045336	IndAlo0045354	4/1/1990	Campbell, D.B., Stereoselectivity in Clinical Pharmacokinetics and Drug Development, 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0036	N/A	IndAlo0045355	IndAlo0045378	1995	Crossley, R., Chirality and the Biological Activity of Drugs, CRC Press (1995)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0037	N/A	IndAlo0001037	IndAlo0001045	3/1/2002	Davies, T.G., et al., Structure-based design of cyclin-dependent kinase inhibitors, 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0038	N/A	IndAlo0079126	IndAlo0079133	11/1/2003	Genuth S., et al., Follow-up Report on the Diagnosis of Diabetes Mellitus, 26(11) Diabetes Care 3160–167 (Nov. 2003)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris

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JTX-0039	N/A	IndAlo0079134	IndAlo0079137	5/1/1999	Gutzwiller, J. et al., Glucagon-Like Peptide-1 Promotes Satiety And Reduces Food Intake In Patients With Diabetes Mellitus Type 2, 276(5) Am. J. Physiol. R1541–4 (May 1999)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0040	N/A	IndAlo0045596	IndAlo0045599	7/1/2003	Higgins, J., Pharmaceutical Preformulation, Today's Chemist at Work 22-26 (July 2003)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0041	N/A	IndAlo0079138	IndAlo0079145	11/1/1998	Holst, J., et al., Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes, 47(11) Diabetes 1663–670 (Nov. 1998)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0042	N/A	IndAlo0079146	IndAlo0079161	2003	Hundal, R., Metformin: New Understandings, New Uses, 63(18) Drugs 1879–894 (2003)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0043	N/A	IndAlo0045600	IndAlo0045608	2002	Hutt, A.J., The Development of Single-Isomer Molecules: Why and How, 7(4 supp. 1) CNS Spect. 14-22 (2002)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0044	N/A	IndAlo0079162	IndAlo0079174	1/16/2002	Inzucchi, S., Oral Antihyperglycemic Therapy For Type 2 Diabetes: Scientific Review, 287(3) JAMA. 360–372 (Jan. 16, 2002)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols

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JTX-0045	N/A	IndAlo0045609	IndAlo0045617	1997	Izumi, T., et al., Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data, 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris; Rebuttal Expert Report of David Nichols
JTX-0046	N/A	N/A	N/A		Manual of Patent Examining Procedure, Ninth Ed., Last Revised January 2018, Section 2143	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0047	N/A	IndAlo0079182	IndAlo0079197	11/30/1999	Mentlein, R., Dipeptidyl-Peptidase IV (CD26)--Role In The Inactivation Of Regulatory Peptides. 85(1) Regul Pept. 9–24 (Nov. 30, 1999)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0048	N/A	IndAlo0079198	IndAlo0079206	2003	Rasmussen H., et al., Crystal Structure of Human Dipeptidyl Peptidase IV/CD26 in Complex with a Substrate Analog, 10(1) Nat. Struct. Biol. 19-25 (Jan. 2003)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0049	N/A	IndAlo0079207	IndAlo0079222	7/1/1997	Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 20(7) Diabetes Care 1183–1197 (Jul. 1997)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0050	N/A	IndAlo0079223	IndAlo0079259	12/1/2003	Setter, S. et al., Metformin Hydrochloride In The Treatment Of Type 2 Diabetes Mellitus: A Clinical Review With A Focus On Dual Therapy, 25(12) Clin Ther. 2991–3026 (Dec. 2003)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0051	N/A	IndAlo0079260	IndAlo0079267	8/12/2000	Stratton, I., Association Of Glycaemia With Macrovascular And Microvascular Complications Of Type 2 Diabetes (UKPDS 35): Prospective Observational Study," 321(7258) Br. Med. J. 405-412 (Aug. 12, 2000)	Opening Expert Report of Dana Ferraris; Reply Expert Report of Dana Ferraris
JTX-0052	Nichols Exhibit 20	IndAlo0079401	IndAlo0079142	1992	Mottola, D., et al., Conformational Analysis of D1 Dopamine Receptor Agonists: Pharmacophore Assessment and Receptor Mapping, 39 J. MED. CHEM. 285-296 (1992)	Reply Expert Report of Dana Ferraris; Deposition of David Nichols
JTX-0053	Nichols Exhibit 21	IndAlo0079439	IndAlo079444	1999	Blair, J., et al., Thieno [3,2-b]- and Thieno [2,3-b]pyrrole Bioisosteric Analgoeis of the Hallucinogen and Serotonin Agonist N, N-Dimethyltryptamine, 42 J. MED. CHEM. 1106-1111 (1999)	Reply Expert Report of Dana Ferraris; Deposition of David Nichols
JTX-0054	N/A	IndAlo0079360	IndAlo79363	2002	Villhauer, E., et al., 1-[2-[5-Cyanopyridin-2-yl]amimo]-ethylamino]acetyl-2-(S)-pyrrolidine-carbonitrile: A Potent, Selective, and Orally Bioavilable Dipeptidyl Peptidase IV Inhibitor with Antihyperglycemic Properties, 45 J. MED. CHEM. 2362-2365 (2002).	Reply Expert Report of Dana Ferraris
JTX-0055	N/A	IndAlo0079413	IndAlo0079422	2003	Senten, K., et al., Design, Synthesis, and SAR of Potent and Selective Dipeptide-Derived Inhibitors for Dipeptidyl Peptidases, 46 J. MED. CHEM. 5005-5014 (2003)	Reply Expert Report of Dana Ferraris

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0056	N/A	IndAlo0079423	IndAlo0079438	2010	Fleming, F., et al., Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore, 53 J. Med. Chem. 7902-7917 (2010)	Reply Expert Report of Dana Ferraris
JTX-0057	N/A	IndAlo0079364	IndAlo0079400	11/20/2009	Bardagi, J., et al., Advances in the Synthesis of 5- and 6-Substituted Uracil Derivatives, 479-514 (Nov. 20, 2009)	Reply Expert Report of Dana Ferraris
JTX-0058	N/A	IndAlo0079445	IndAlo0079502	10/5/1999	PCT Publication WO 95/26325 (Publication date : Oct. 5, 1995)	Reply Expert Report of Dana Ferraris
JTX-0059	N/A	N/A	N/A	2013	Highlights of Prescribing Information – KAZANO (alogliptin and metformin HCL) tablets, for oral use. Initial U.S. Approval: 2013	Rebuttal Expert Report of David Nichols
JTX-0060	N/A	N/A	N/A	2013	Highlights of Prescribing Information – NESINA (alogliptin) tablets. Initial U.S. Approval: 2013	Rebuttal Expert Report of David Nichols
JTX-0061	N/A	TAK-ALOG00024699	TAK-ALOG00024717	2013	Highlights of Prescribing Information – OSENI (alogliptin and pioglitazone) tablets. Initial U.S. Approval: 2013	Rebuttal Expert Report of David Nichols
JTX-0062	N/A	IndAlo0000962	IndAlo0000965	2/1/2003	"Astex, Structural Genomix, and Syrrx: I Can See Clearly Now: Structural Biology and Drug Discovery", 10 Chem. & Bio. 95-98 (Feb. 2003)	Rebuttal Expert Report of David Nichols
JTX-0063	N/A	IndAlo0001071	IndAlo0001106		Indoco's ANDA excerpt – Highlights of Prescribing Information	Rebuttal Expert Report of David Nichols
JTX-0064	N/A	TAK-ALOG00014232	TAK-ALOG00016141	5/31/2016	Takeda, Development Safety Update Report for Alogliptin Benzoate (Fifth	Rebuttal Expert Report of David Nichols

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
					Report) May 31, 2016	
JTX-0065	N/A	TAK-ALOG000186128	TAK-ALOG000186268	3/15/2004	U.S. Provisional application 60/553,571 (the '571 provisional"), filed on March 15, 2004	Rebuttal Expert Report of David Nichols
JTX-0066	N/A	TAK-ALOG000186270	TAK-ALOG000186434	11/18/2004	U.S. Provisional application 60/629,524 (the'524 provisional"), filed on November 18, 2004	Rebuttal Expert Report of David Nichols
JTX-0067	N/A	TAK-ALOG00127292	TAK-ALOG00127298	2005	Lankas, George R. et al., "Dipeptidyl Peptidase IV Inhibition for the Treatment of Type 2 Diabetes', 54 DIABETES 2988 (2005)	Rebuttal Expert Report of David Nichols
JTX-0068	N/A	TAK-ALOG00149856	TAK-ALOG0014957	7/20/2004	Itinerary for Syrrx, Inc. and PPD, Inc. (July 20, 2004)	Rebuttal Expert Report of David Nichols
JTX-0069	N/A	TAK-ALOG00149878	TAK-ALOG00149893	1/20/2004	DRAFT Minutes of PPD – Syrrx JOC meeting (January 20, 2004)	Rebuttal Expert Report of David Nichols
JTX-0070	N/A	TAK-ALOG00150359	TAK-ALOG00150372	2012	Agrawal, Ritesh et al., "Novel Serine Protease Dipeptidyl Peptidase IV Inhibitor: Alogliptin", 12 MINI-REVIEWS IN MED. CHEM. 1345, 1348 (2012)	Rebuttal Expert Report of David Nichols
JTX-0071	N/A	TAK-ALOG00150373	TAK-ALOG00150423	1996	Bighley, L.D. Berge, S.M. & Monkhouse, D.C., "Salt Forms of Drugs and Absorption", Encyclopedia Pharm. Tech. 453 (1996)	Rebuttal Expert Report of David Nichols
JTX-0072	N/A	TAK-ALOG00150435	TAK-ALOG00150445	2017	Classen, Daniel O. et al., "Indirect Tolerability Comparison of Deutetrabenazine and Tetrabenazine for Huntington Disease", 4:3 J. CLINICAL	Rebuttal Expert Report of David Nichols

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
					MOVEMENT DISORDERS 1 (2017)	
JTX-0073	Nichols Exhibit 19	TAK-ALOG00150506	TAK-ALOG00150526	2004	Dror, Oranit et al., "Predicting Molecular Interactions in silico: 1. A Guide to Pharmacophore Identification and its Applications to Drug Design", 11 CURRENT MED. CHEM. 71, 71 (2004)	Rebuttal Expert Report of David Nichols; Deposition of David Nichols
JTX-0074	N/A	TAK-ALOG00150633	TAK-ALOG00150641	2008	Bumsup, Lee et al., "Pharmacokinetic, Pharmacodynamic, and Efficacy Profiles of Alogliptin, a Novel Inhibitor of Dipeptidyl Peptidase-4, in Rats, Dogs, and Monkeys', 589 EUR. J. PHARMACOLOGY 306 (2008)	Rebuttal Expert Report of David Nichols;
JTX-0075	N/A	TAK-ALOG00150734	TAK-ALOG00150756	2001	Lipinski, Christopher A. et al., "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings", 46 Advanced Drug Delivery Reviews 3–25 (2001)	Rebuttal Expert Report of David Nichols
JTX-0076	N/A	TAK-ALOG00150909	TAK-ALOG00150912	2001	Tagat, Jayaram R. et al., "Piperazine-Based CCR5 Antagonists as HIV-1 Inhibitors. II. Discovery of 1-[(2,4-Dimethyl-3-pyridinyl)carbonyl]-4-methyl-4-[3(S)-methyl-4-[1(S)-[4-(trifluoromethyl)phenyl]ethyl]-1-piperazinyl]-piperidine N1-Oxide (Sch-350634), an Orally Bioavailable, Potent CCR5 Antagonist", 44 J. MED. CHEM. 3343 (2001)	Rebuttal Expert Report of David Nichols

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JTX-0077	N/A	TAK-ALOG00151016	TAK-ALOG00151023	1997	Victor, Frantz et al., "Synthesis, Antiviral Activity, and Biological Properties of Vinylacetylene Analogs of Enviroxime", 40 J. MED. CHEM. 1511 (1997)	Rebuttal Expert Report of David Nichols
JTX-0078	N/A	TAK-ALOG_00153045	TAK-ALOG_00153238		Feng, Jun, LABORATORY NOTEBOOK NO. 366	Rebuttal Expert Report of David Nichols
JTX-0079	N/A	TAK-ALOG_00017055	TAK-ALOG_00017206	1/6/2006	Takeda PRE-IND Briefing Document submitted to FDA re: SYR-322-4833 Fixed-Dose Combination Product dated January 6, 2006	Rebuttal Expert Report of David Nichols
JTX-0080	N/A	TAK-ALOG00186496	TAK-ALOG00186506	1982	Ogilvie, Kelvin K. et al., "Biologically Active Acyclonucleoside Analogues II: The Synthesis of 9-[[2-hydroxy-1-(hydroxymethyl) ethoxy] methyl] guanine (BIOLF-62)", 60 CAN. J. CHEM. 3005 (1982)	Rebuttal Expert Report of David Nichols
JTX-0081	N/A	TAK-ALOG00368225	TAK-ALOG00368231	2006	Green, Brain D. et al., "Dipeptidyl Peptidase IV (DPP IV) Inhibitors: A Newly Emerging Drug Class for the Treatment of Type 2 Diabetes", 3 DIABETES AND VASCULAR DISEASE RESEARCH 159 (2006)	Rebuttal Expert Report of David Nichols
JTX-0082	N/A	TAK-ALOG00413769	TAK-ALOG00413787	1999	Erkkila, Katheryn E. et al., "Recognition and Reaction of Metallointercalators with DNA", 99 Chem. Rev. 2777, 2779 (1999)	Rebuttal Expert Report of David Nichols

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
JTX-0083	N/A	TAK-ALOG00413788	TAK-ALOG00413788	12/11/2017	DRUGS.COM, "Galvus Approval Status", https://www.drugs.com/history/galvus.html (last visited Dec. 11, 2017)	Rebuttal Expert Report of David Nichols
JTX-0084	N/A	TAK-ALOG00413789	TAK-ALOG00413789	7/18/2019	"FDA Approved Drugs – Structure Search", http://www.cheminfo.org/Chemistry/Database/DrugBank/Structure_search/index.html (last visited July 18, 2019)	Rebuttal Expert Report of David Nichols
JTX-0085	N/A	TAK-ALOG0000413790	TAK-ALOG00413793	7/17/2019	Drugbank, "Statistics", https://www.drugbank.ca/stats (last visited July 17, 2019)	Rebuttal Expert Report of David Nichols
JTX-0086	Nichols Exhibit 11	TAK-ALOG00413794	TAK-ALOG00413804	1990	Univ. of Cal School of Pharmacy, "Peptide and Protein Drug Delivery, Chapter 2.: Synthesis of Peptides and Proteins by Chemical and Biotechnological Means", 95-103 (Vincent H. L. Lee, et al. 1990)	Rebuttal Expert Report of David Nichols; Deposition of David Nichols
JTX-0087	N/A	TAK-ALOG00413805	TAK-ALOG00413809	2007	Oballa, Renata M. et al., "A generally applicable method for assessing the electrophilicity and reactivity of diverse nitrile-containing compounds", Bioorganic & Medicinal Chemistry Letters 17 998–1002 (2007)	Rebuttal Expert Report of David Nichols
JTX-0088	N/A	TAK-ALOG00149830	TAK-ALOG00149838	12/19/2003	Albany Molecular Research, Inc., Project Update, Syrrx Salt Selection, Project Number 2117 (December 19, 2003)	Rebuttal Expert Report of David Nichols

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JTX-0089	N/A	TAK-ALOG00150290	TAK-ALOG00150293	2007	Feng, Jun et al., "Discovery of Alogliptin: A Potent, Selective, Bioavailable, and Efficacious Inhibitor of Dipeptidyl Peptidase IV", 50 J. Med. Chem. 2297-2300 (2007)	Rebuttal Expert Report of David Nichols
JTX-0090	N/A	TOR-NESINA00126351	TOR-NESINA00126360	2001	Villhauer, Edward B. "Chapter 19. DPP-IV Inhibition and Therapeutic Potential", ANNUAL REPORTS IN MEDICINAL CHEMISTRY 191, 194 (2001)	Rebuttal Expert Report of David Nichols
JTX-0091	N/A	TOR-NESINA00126407	TOR-NESINA00126501	2002	Stahl et al., Eds., Handbook of Pharmaceutical Salts 273 (2002)	Rebuttal Expert Report of David Nichols
JTX-0092	Nichols Exhibit 2	N/A	N/A	7/2/2002	US Patent 6,413,977 B1	Deposition of David Nichols
JTX-0093	Nichols Exhibit 3	N/A	N/A	7/12/2012	Juncosa, Jose I., et al. "Extensive Rigid Analogue Design Maps the Binding Conformation of Potent N-Benzylphenethylamine 5-HT2A Serotonin Receptor Agonist Ligands" ACS Chem. Neurosci., A-N (2012)	Deposition of David Nichols
JTX-0094	Ferraris Exhibit 10	N/A	N/A	9/17/2004	Ferraris, Dana et al, "Ketopyrrolidines and Ketoazetidines as Potent Dipeptidyl peptidase IV (DPP IV) Inhibitors"	Deposition of Dana Ferraris
JTX-0095	Ferraris Exhibit 11	N/A	N/A	2007	Ferraris, Dana et al, "Azetidine-Based Inhibitors of Dipeptidyl Peptidase IV (DPP IV)	Deposition of Dana Ferraris
JTX-0096	Ferraris Exhibit 12	N/A	N/A		Preferred Compound	Deposition of Dana Ferraris
JTX-0097	Ferraris Exhibit 13	N/A	N/A	May-11	Highlights of Prescribing Information	Deposition of Dana Ferraris

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
					for Tradjenta	
JTX-0098	N/A	N/A	N/A	6/7/2019	Exhibit A Materials Considered - Opening Expert Report of David Rotella	
JTX-0099	Rotella Exhibit 2	N/A	N/A	6/7/2019	Exhibit B CV of David Rotella - Opening Expert Report of David Rotella	
JTX-0100	N/A	N/A	N/A	8/23/2019	Exhibit A Materials Considered - Reply Expert Report of David Rotella	
JTX-0101	N/A	N/A	N/A	6/14/2019	Exhibit A Materials Considered - Opening Expert Report of Dana Ferraris, Ph.D., MBA	
JTX-0102	N/A	N/A	N/A	6/14/2019	Exhibit B CV of Dana Ferraris, Ph.D., MBA - - Opening Expert Report of Dana Ferraris, Ph.D., MBA	
JTX-0103	N/A	N/A	N/A	8/23/2019	Exhibit A Materials Considered - Reply Expert Report of Dana Ferraris, Ph.D., MBA	
JTX-0104	N/A	N/A	N/A	6/5/2019	Appendix A CV of David Earl Nichols - Opening Expert Report of David E. Nichols	
JTX-0105	N/A	N/A	N/A	6/5/2019	Appendix B Actions in the past four years - Opening Expert Report of David Nichols	
JTX-0106	N/A	N/A	N/A	7/19/2019	Appendix A CV of David Earl Nichols - Rebuttal Expert Report of David E.	

Trial Exhibit Number	Deposition Exhibit No.	Beg Bates	End Bates	Doc Date	Description	Source
					Nichols	
JTX-0107	N/A	N/A	N/A	7/19/2019	Appendix B Actions in the past four years - Rebuttal Expert Report of David Nichols	
JTX-0108	N/A	N/A	N/A	7/19/2019	Appendix C Material Considered - Rebuttal Expert Report of David Nichols	

TAB 18

18. PLAINTIFFS' LEGAL ISSUES

This statement is based on the arguments Plaintiffs expect to make at trial, as well as their understanding of the arguments that Defendants are likely to make, and on the current status of the case and the Court's rulings to date. Plaintiffs reserve the right to modify or amend this Statement to the extent necessary to reflect any future rulings by the Court, and to supplement or amend this Statement to fairly respond to any new issues that Defendants may raise. To the extent Plaintiffs' statement of contested facts that remain to be litigated at trial contain issues of law, those legal issues are incorporated by reference. Plaintiffs incorporate by reference their expert reports, pleadings, contentions, and interrogatory responses in support of any proof to be presented by expert testimony that Plaintiffs will offer at trial or in their pretrial and/or post-trial briefs.

Defendants Torrent and Indoco have stipulated that their respective proposed generic Alogliptin products infringe claims 4 and 12 of the '689 patent. (*See* Dkt. No. 81, Civ. No. 17-3186, Dkt. No. 56, Civ. No. 17-7301.) Therefore, Plaintiffs need not prove infringement at trial, and judgment of infringement should be entered in Plaintiffs' favor.

Moreover, federal statute mandates that a "patent shall be presumed valid." 35 U.S.C. § 282(a). Thus, the burden that Defendants bear to prove their obviousness claims and overcome that presumption is the highest in civil law – "clear and convincing evidence." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).[3] Defendants' challenges are based on prior art and, where a prior-art reference is listed on the face of a patent (as is the case for Defendants' primary

[3] This applies equally to Defendants' obviousness-type double patenting claim. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991) ("Double patenting is an affirmative defense," to be proven "by clear and convincing evidence, a heavy and unshifting burden.").

references), "the examiner is presumed to have considered it," and the challenger has the "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." *Shire, LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (internal quotations omitted). This presumption is particularly salient here, as patents are issued by "examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." *Id.* (internal quotations omitted).

The type of challenge made here by Defendants is extraordinary, as obviousness attacks directed to compound patents covering new chemical entities are routinely rejected. *See, e.g., Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (obviousness rejected where lead compound pathway required a POSA to "drop the very feature" identified as advantageous); *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("prior art offer[ed] no suggestion to pursue the particular order of manipulating parts of the compounds"); *Eli Lilly & Co. v. Zenith/ Goldline Pharms., Inc.*, 471 F.3d 1369, 1378-9 (Fed. Cir. 2006) (obviousness rejected where proposed lead was adjacent homolog of claimed compound, but a different compound was identified in the art as "particularly active"); *Daiichi Sankyo Co. Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1351 (Fed. Cir. 2010) (obviousness rejected in view of insufficient evidence a POSA would choose the proposed lead compound "over other better-studied ARBs with greater potency" and where most of the disclosed compounds shared common features different from that compound); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) (affirming judgment of nonobviousness of aripiprazole over § 103 and obviousness-type double patenting arguments). Indeed, Takeda has

found only one case in the history of Hatch-Waxman jurisprudence (35 years) that has ever affirmed a determination of obviousness for a patent claiming a new chemical entity. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 769 F.3d 1339, 1345-6 (Fed. Cir. 2014). And in that case – unlike in this case – the patentee conceded that the proposed compound was "actually being used as a lead compound at the time of the [drug's] invention" and that a POSA could be led to the drug via "conservative changes" to the lead compound's structure. *See Bristol-Myers*, 769 F.3d at 1345-46.

I. OBVIOUSNESS UNDER 35 U.S.C. § 103(a)

The first legal issue that the Court must determine is whether Defendants can prove by clear and convincing evidence that claims 4 and 12 of the '689 patent are invalid for obviousness under 35 U.S.C. § 103 over the prior art references set forth in Dr. Ferraris' June 14 and August 23, 2009 expert reports.

The analysis this Court must apply to Defendants' statutory obviousness theory is clear: "[W]hether a new chemical compound would have been *prima facie* obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka*, 678 F.3d at 1291. To meet this first prong, the infringer must "prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select [the lead compound] from the panoply of known compounds in the prior art." *Otsuka*, Id. at 1292. A lead compound must be more than just "known as a compound;" it must be "a known active drug substance." *Shire*, 2014 WL 2861430, at *17. Further, "Defendants must show by clear and convincing evidence" that the compound

chosen "would be most promising to modify in order to … obtain a compound with better activity." *Pfizer Inc. v. IVAX Pharm., Inc.*, 2010 U.S. Dist. LEXIS 6002, at *24-25 (D.N.J. Jan. 20, 2010) (*citing Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357-58 (Fed. Cir. 2007)).

The Federal Circuit has made clear that the use of hindsight in choosing a lead compound is impermissible. "Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharms. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019); *see also InTouch Techs., Inc. v. VGo Communs., Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) ("hindsight analysis is inappropriate because obviousness must be assessed at the time the invention was made."); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *Pfizer Inc.*, 2010 U.S. Dist. LEXIS 6002, at *14 (a finding of obviousness, "'cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.'") (*citing Crown Operations Int'l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002)).

Further, it is fatal to an expert's credibility where he or she does not "perform an analysis of the art as a whole" when choosing a lead compound. *AstraZeneca AB v. Aurobindo Pharma Ltd.*, 232 F. Supp. 3d 636, 646-47 (D. Del. 2017). It is insufficient for the expert to "look[] to a selection of prior art handpicked by [] counsel in order to select the compound for his obviousness analysis." *Id.* And this court has held that an expert cannot ignore other potential lead compounds with structures that he or she perceived would require more modification to

achieve the claimed compound. *See e.g., Merck Sharp & Dohme Pharm. v. Teva Pharm. USA, Inc.*, 2009 U.S. Dist. LEXIS 131869, at *141-42 (D.N.J. Aug. 19, 2009) ("in abandoning these other compounds … [the expert] impermissibly used the benefit of hindsight to eliminate compounds with structures that he perceived would require more modifications to get to montelukast.");

If, and only if, there is a proper lead compound, the court turns to the second step, in which it determines whether the infringer has shown that "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success" – again by "clear and convincing evidence." *Otsuka*, 678 F.3d at 1292 (citations omitted); *accord Novartis Pharm. Corp. v. W. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019). "To have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (citations omitted).

II. OBVIOUSNESS-TYPE DOUBLE PATENTING

The second legal issue that the Court must determine is whether Defendants can prove by clear and convincing evidence that claims 4 and 12 of the '689 Patent are invalid for obviousness-type double patenting over claim 162 of U.S. Patent No. 7,723,444 (the "Feng patent") in view of Kim et al., "Anti-diabetic activity of Constituents of Lycii Fructus," The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("Kim 1998") and the common knowledge of a POSA related to the state of the art as of November 18, 2004.

To analyze obviousness-type double patenting, a court must first "construe[] the claims in the earlier patent and the claims in the later patent and determine[] the differences." *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1323 (Fed. Cir. 2018) (internal quotations omitted). "The question, thus, is whether the later invention is a '***slight variant***' of the earlier." *Pfizer, Inc. v. Teva Pharms. USA. Inc.*, 803 F.Supp.2d 409, 448 (E.D. Va. 2011) (emphasis added) (citing *Geneva Pharms, Inc. v. GlaxoSmithKline P.L.C.*, 349 F.3d 1373, 1378 (Fed. Cir. 2003)). The "differences" between the prior art and the claimed invention "cannot be considered in isolation—the claims must be considered as a whole." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1377 (Fed. Cir. 2012).

The second part of the analysis is "analogous to the obviousness inquiry under 35 U.S.C. § 103." *UCB*, 890 F.3d at 1323. It "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." *See Eli Lilly*, 689 F.3d at 1378 (rejecting obviousness-type double patenting where the proposed modification was not proved to be "the one, among all the possibilities, that would have been successfully pursued" given the many "opportunities for modification"). Indeed, "[t]here is no other way to consider the obviousness of a compound B over compound A without considering whether [a POSA] would have had reason to modify A to make B." *Otsuka*, 678 F.3d at 1298. Even compounds that differ only slightly in structure may not be obvious variants. *See, e.g.*, *Eli Lilly*, 689 F.3d at 1377 (difference in ring structure, but same substituents); *Bayer AG v. Dr. Reddy's Labs., Ltd.*, 518 F.Supp.2d 617 (D. Del. 2007) (rejecting claim even where "[t]he only difference between" the claims was "the 8-position substituent"). The use of hindsight is similarly prohibited in the double patenting context. *See*

e.g., Eli Lilly & Co. v. Teva Parenteral Meds., Inc., No. 08-335-GMS, 2011 U.S. Dist. LEXIS 83124 (D. Del. July 28, 2011); *FilmTec Corp. v. Hydranautics*, Case No. 90-563 GT (M), 1991 U.S. Dist. LEXIS 13495 (S.D. Cal. Aug. 30, 1991).

III. PRIORITY DATE

The third legal issue that the Court must determine is whether Defendants can prove by clear and convincing evidence that claims 4 and 12 of the '689 patent are not entitled to their claimed priority date of no later than March 15, 2004 – the date of the provisional application. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1328 (Fed. Cir. 2008) (Defendant must "convince the court that [Plaintiff] is not entitled to the benefit of the earlier filing date" and "if the court is not persuaded by clear and convincing evidence that [Defendant] is correct, [Defendant] has failed to carry its ultimate burden of persuasion, and its defense of invalidity … fails.")

Claims enjoy the earlier filing date if the provisional application provided adequate written description under 35 U.S.C. § 112, P 1. *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1359 (Fed. Cir. 2010). "The 'prior application itself must describe an invention . . . in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.'" *Id.* (*citing Lockwood v. Am. Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)).

IV. REMEDIES

The fourth legal issue that the Court must determine is whether Plaintiffs are entitled to a judgment order that the claims of the '689 patent are valid and enforceable.

The fifth legal issue that the Court must determine is whether Plaintiffs are entitled to a judgment pursuant to 35 U.S.C. § 271(e)(4)(a) ordering that the effective date of any approval of Defendants' ANDAs be a date that is not earlier than the expiration date of the '689 patent (June 27, 2028) or any other exclusivity to which Plaintiffs are or become entitled.

The sixth legal issue that the Court must determine is whether Plaintiffs are entitled to a determination of costs and expenses in this action.

Plaintiffs submit these legal issues based on the status of the claims and defenses currently asserted in the action and reserve their right to modify, supplement, or amend these exhibits as a result of, for example, resolution of pending issues or motions, further discovery, reductions in claims and defenses by the parties to streamline the case for trial, or a decision on any motion by the Court.

TAB 19

19. DEFENDANTS' LEGAL ISSUES

DEFENDANTS' LEGAL ISSUES

Defendants Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc. (collectively, "Torrent") together with Defendant Indoco Remedies Ltd. ("Indoco") (collectively with Torrent, "Defendants") submit the following statement of legal issues to be litigated at trial ("Statement"). Headings and subheadings are for organizational purposes only, not an admission that any facts under a particular heading are relevant only to that section.

This statement is based on the arguments Defendants expect to make as well as their understanding of the argument that Plaintiffs are likely to make, and on the current status of the case and the Court's rulings to date. Defendants reserve the right to modify or amend this Statement to the extent necessary to reflect any future rulings by the Court, and to supplement or amend this Statement to fairly respond to any new issues that Plaintiffs may raise. To the extent Defendants' statement of contested facts that remain to be litigated at trial, which is submitted as Tab 7, contain issues of law, those legal issues are incorporated by reference. Finally, Defendants incorporate by reference their expert reports, pleadings, contentions, and interrogatory responses in support of any proof to be presented by expert testimony that Torrent and Indoco will offer at trial or in their pretrial and/or post-trial briefs.

I. OBVIOUSNESS-TYPE DOUBLE PATENTING

The first legal issue that the Court must determine is whether Defendants have proven by clear and convincing evidence that claims 4 and 12 of the '689 Patent are invalid for obviousness-type double patenting over claim 162 of U.S. Patent No. 7,723,444 (the "Feng patent") in view of Kim et al., "Anti-diabetic activity of Constituents of Lycii Fructus," The

Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) ("Kim 1998") and the common knowledge of a POSA related to the state of the art as of November 18, 2004 as set forth in the opening and reply expert reports of Dr. David P. Rotella.

Obviousness-type double patenting is a "judicially created doctrine adopted to prevent claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection.'" *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1352 (Fed. Cir. 2009) (citing *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1373 (Fed. Cir. 2005)). Double patenting is a question of law. *Sun Pharm. Indus. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010). Analyzing claims for obviousness-type double patenting requires comparing "claims in an earlier patent to claims in a later patent or application." *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377 n.1 (Fed. Cir. 2003). Thus, the starting point in such an analysis is the reference claims of the earlier patent.

This requires a two-step analysis, first, "the court 'construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences.' Second, the court 'determines whether those differences render the claims patentably distinct.'" *Sun Pharm. Indus.*, 611 F.3d at 1385. "A later claim that is not patentably distinct from, i.e., is 'obvious over or anticipated by,' an earlier claim is invalid for obviousness-type double patenting." *Id.* (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001)).

In construing claims, courts must first examine the "intrinsic evidence," which includes the language of the claims, the prosecution history, and the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). While the reference patent's specification

cannot be used as prior art in a double patenting analysis, the disclosure in the specification of the earlier patent is relevant to claim construction and a "claim must be read in view of the specification of which they are a part." *Phillips*, 415 F.3d at 1315 (citations omitted); *Eli Lilly & Co. v. Teva Parenteral Meds.*, Inc., 689 F.3d 1368, 1378-79 (Fed. Cir. 2012); *see also Sun Pharm.*, 611 F.3d at 1388 (explaining that, "where a patent claims a compound, a court performing an obviousness-type double patenting analysis should examine the specification to ascertain the coverage of the claim"). "[I]t is also well settled that we may look to a reference patent's disclosures of utility to determine the question of obviousness," i.e., "to answer the question whether claims merely define an obvious variation of what is earlier disclosed and claimed." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1380-81 (Fed. Cir. 2014) (internal citations omitted)

Step two of the obvious-type double patenting "is analogous to an obviousness analysis under 35 U.S.C. § 103." *Abbvie Inc.*, 764 F.3d at 1378 (quoting *Amgen Inc.*, 580 F.3d at 1361). "Thus, if the later expiring patent is merely an obvious variation of an invention disclosed and claimed in the [reference] patent, the later expiring patent is invalid for obviousness-type double patenting." *Abbvie Inc.*, 764 F.3d at 1379 (quotations omitted).

In the context of claimed chemical compounds based on obviousness-type double patenting, "the issue is not whether a skilled artisan would have selected the earlier compound as a lead compound." *Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012). "This is because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, lead compound or not." *Id.* The analysis is "whether one of ordinary skill in the art would have had reason or motivation to

modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success." *Id.* at 1298. Thus, the earlier claimed compound from the alleged invalidating reference is the starting point for the obviousness analysis.

Inquiry into secondary considerations is not required in every obviousness-type double patenting analysis. *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012). Evidence of secondary considerations may be considered when offered in an obviousnesstype double patenting analysis. (*Id.*) To overcome a prima facie case of obviousness, the patentee must establish a nexus between the secondary considerations, such as unexpected results, and the claimed invention. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1245-46 (Fed. Cir. 2010); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

II. OBVIOUSNESS UNDER 35 U.S.C. § 103(a)

The second legal issue that the Court must determine is whether Defendants have proven by clear and convincing evidence that claims 4 and 12 of the '689 patent are invalid for obviousness under 35 U.S.C. § 103 over the prior art references set forth in Dr. Ferraris' June 14 and August 23, 2009 expert reports.

Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The teachings of a prior art reference are underlying factual questions in the obviousness inquiry. *Para-Ordnance Mfg., Inc. v. SGS Imp. Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995).

With respect to determining whether there exists a motivation to combine prior art references, the U.S. Supreme Court held that, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)

To determine whether there was an "apparent reason" to combine the known elements in the way a patent claims, it may be necessary, "to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art." *Id.* It is not necessary, however, that the references be combined for the same reasons as the inventor. Lack of predictability in results does not alone negate the motivation to combine references as the "expectation of success need only be reasonable, not absolute."

In determining the level of ordinary skill in the art, a court may consider several factors. These include the kinds of problems existing in the art, the known solutions to the problems, the rate at which new inventions are made in the field, the complexity of the technology and the educational level of working scientists in the field. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Amazon.com v. Barnesandnoble.com*, 239 F.3d 1343 (Fed. Cir. 2001) ("[T]he relevant inquiry is what a hypothetical ordinary skilled artisan would have gleaned from the cited

references at the time that the patent application … was filed"); *Ryko Mfg. Co. v. Nu-Star Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991).

As set forth in the Manual of Patent Examining Procedure (MPEP), and as articulated in *KSR*, exemplary rationales that may support a conclusion of obviousness include:

Combining prior art elements according to known methods to yield predictable results;

Simple substitution of one known element for another to obtain predictable results;

Use of known technique to improve similar devices (methods, or products) in the same way;

Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

"obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

M.P.E.P. § 2143; *see also KSR,* 550 U.S. at 416-421.

A prima facie case of obviousness is created when "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). "Obviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound." *Altana Pharama AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009). The prior art must provide "a reasonable expectation of success, [but] not absolute predictability."

Eli Lilly and Co. v. Zenith Goldline Pharama, Inc., 471 F.3d 1369, 1377 (2006) (quoting *In re Longhi*, 759 F.2d 887, 896 (Fed. Cir. 1985). Motivation to combine references "does not have to be found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (internal quotations omitted).

The lead compound analysis has been used to determine obviousness in context of claims to a specific compound. *Ex Parte Argade*, 2016 WL 4254893, at *10 (PTAB 2016). The Federal Circuit created the so-called Lead Compound Analysis ("LCA") to determine whether a prior art compound qualifies as a starting point to prove obviousness. The LCA requires a two-step inquiry. *Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).

A court first determines "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* A lead compound under the LCA is "a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity." *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The LCA requires some motivation based on the prior art to qualify as a lead compound, mere structural similarity is not enough. *Otsuka*, 678 F.3d at 1292.

"In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Id.* These properties

may include "positive attributes such as activity and potency," "adverse effects such as toxicity," and other "relevant characteristics in evidence." *Id.*

A court then determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* Similar to the first step, the court looks to motivation "from any number of sources and need not necessarily be explicit in the prior art. *Id.*

Establishment of a prima facie case of obviousness may be negated by a showing of "secondary considerations" of nonobviousness. *See Graham*, 383 U.S. 17-18. These factors include: 1) long-felt and unmet need; 2) failure of others; 3) industry acclaim; 4) commercial success; and 5) unexpected results. Generally, the secondary considerations of nonobviousness provide motivation for others to enter the field. Any probative evidence, however, of secondary considerations must have a sufficient "nexus" with the claimed invention. *Stratoflex, Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). For example, evidence of long-felt need must be derived from commercial embodiments that incorporate all elements of the claimed invention. *Id.*

III. RELIEF

The fourth legal issue that the Court must determine is whether Defendants are entitled to a judgement declaring that claims 4 and 12 of the '689 patent are invalid for obviousness-type double patenting and/or obviousness under 35 U.S.C. §103.

The fifth legal issue that the Court must determine is whether Defendants are entitled to costs and expenses in this action.

Defendants submit these legal issues based on the status of the claims and defenses currently asserted in the action and reserve their right to modify, supplement, or amend these exhibits as a result of, for example, resolution of pending issues or motions, further discovery, reductions in claims and defenses by the parties to streamline the case for trial, or a decision on any motion by the Court.

TAB 20

20. MISCELLANEOUS (Set forth any matters which require action by, or should be brought to the attention of, the Court.)

A. Order of Proof

The parties proposed the following order of proof for trial: because Defendants have the burden of proof on the issues for trial regarding invalidity, Defendants will go first followed by Plaintiffs.

a. Opening statements will be delivered in the following order: Defendants (either separately or collectively by an attorney for either Torrent or Indoco) will deliver opening statements first followed by Plaintiffs.

b. Defendants shall then present their affirmative case on invalidity.

c. Upon conclusion of Defendants' testimony and evidence on those issues, Plaintiffs shall present their rebuttal testimony on validity, including any objective indicia of nonobviousness.

d. Upon conclusion of Plaintiffs' testimony and evidence on validity and objective indicia of nonobviousness, Defendants shall present their rebuttal testimony and evidence of objective indicia of nonobviousness.

e. To the extent any witnesses must be taken out of the above recited order, the parties will work in good faith to accommodate those needs.

f. The parties will follow the Court's guidance as to the need for closing statements and the order of presentation thereof.

B. Stipulated Procedures

a. Exhibits

1. Evidence in lieu of certified copies thereof, subject to all other objections, which might be made the '689 patent and U.S. Patent No. 7,723,344, and the contents of their file histories, may be offered and received in the circumstances it would be unfair to admit the copy in lieu of the original. Legible copies are admissible to the same extent as an original unless a genuine question is raised as to the authenticity of the original, or illegible copies of documents may be offered and received in evidence to the same to the admissibility of certified copies.

2. Each exhibit list contains exhibits that a party may present at trial, other than exhibits solely for cross examination and/or impeachment. The parties reserve the right to reasonably supplement and/or amend their respective exhibit lists in advance of trial. However, after October 25, 2019, the parties may only supplement their respective exhibit lists on a showing of good cause. Each exhibit list may contain some exhibits that may be admissible solely for cross examination and/or impeachment or solely for other limited purposes. Such exhibits used for cross examination and/or impeachment may be admitted into evidence subject to the Federal Rules of Evidence or other applicable principles. The parties reserve the right to introduce, use, and offer summary exhibits and demonstratives, as permitted under the Federal Rules of Evidence, that are not identified on their respective exhibit lists in accordance with the agreement and schedule set forth below.

3. For supplemental or amended exhibits added to the parties' exhibit lists pursuant to the preceding paragraph, the parties will identify and state the basis or bases for any objections to any supplemental or amended exhibit within two (2) days of receiving the supplemental or amended exhibits from the proffering party. Accordingly, the parties agree that failing to set

forth an objection and the reason for said objection in the Pretrial Order does not constitute a waiver of the objection.

4. Neither party will remove a document once it has been added to a side's exhibit list without agreement from the other side, unless it provides the other side the opportunity to add the document to its exhibit list.

5. The parties agree that any description of a document on an exhibit list is provided for convenience only and shall not be used as an admission or otherwise as evidence regarding the listed document or any other listed document.

6. The parties further agree that the listing of a document on a party's exhibit list is not an admission that such document is relevant or admissible when offered by the opposing party for the purpose that the opposing party wishes to admit the document. Each party reserves the right to object to the relevance or admissibility of any evidence offered by another party, at the time such evidence is offered, in view of the specific context in which such evidence is offered.

7. Each party reserves the right to offer exhibits set forth in the opposing party's exhibit list, even if not set forth in its own exhibit list. All objections to such exhibits are preserved, regardless of whether such exhibits also appear on the objecting party's exhibit list. Any exhibit, once admitted at trial, may be used equally by any party for any proper purpose, subject to any limitations as to its admission into evidence.

8. Any document shall be deemed to be authentic absent a specific authenticity objection set forth in Tab 15 or Tab 16 by the parties.

9. Unless otherwise agreed to by the parties during trial, the parties will provide to each other's counsel of record via email a written list of exhibits, by exhibit number, for each witness that it intends to call in Court by 7:00 pm (EST) one (1) calendar day before the day the witness is expected to testify. Objections to any of the disclosed exhibits shall be made no later than 9:00 pm (EST) one (1) calendar day before their intended use, and the parties shall meet and confer at or before 10:00 pm (EST) that same evening to resolve such objections. For example, and to avoid any doubt, if a witness is expected to testify on Monday, November 4, 2019, then the party calling the witness must provide a written list of exhibits, by exhibit number to the other party's counsel of record by 7:00 pm (EST) on Sunday, November 3, 2019, with any objections and a meet-and-confer to discuss such objections due by 9:00 pm (EST) and 10:00 pm (EST), respectively. Any objections to any trial exhibits that are maintained following the meet-and-confer process may be taken up with the Court prior to the witness's testimony or as otherwise directed by the Court.

10. The advance notification provisions for exhibits intended for use in direct examination do not apply to exhibits used during opening statements, to exhibits used during closing arguments (if allowed), or to exhibits used during cross-examination (*i.e.*, notice shall only be given in accordance with the advance notice provisions for exhibits used for direct examination of witnesses).

11. Binders containing copies of exhibits for planned use during direct examination of a witness shall be exchanged at the beginning of the examination of the witness. A party shall not be precluded from using a document for cross examination for the sole reason that it was not

provided by the other side before cross examination of the witness or not listed on the trial exhibit list.

12. The demonstratives the parties intend to use at trial do not need to be described or included on the respective lists of trial exhibits.

b. Demonstratives

1. The parties will provide to each other's counsel of record via email any demonstrative exhibits (in color as applicable) they anticipate using on direct examination of a witness at trial no later than 7:00 p.m. (EST) one (1) calendar day before the demonstrative is to be used at trial. Any objections to demonstrative exhibits shall be made by 9:00 p.m. (EST) that same day, and the parties shall meet and confer by 10:00 p.m. (EST) that same day to resolve such objections. Any disputes as to demonstrative exhibits shall be raised with the Court as appropriate before trial resumes on the day of their anticipated use. There is no requirement to provide demonstratives for use on cross examination prior to their use at trial.

2. The parties will exchange demonstrative exhibits (in color as applicable) for opening statements by 7:00 p.m. (EST) one (1) calendar day before opening statements. Any objections to demonstrative exhibits for opening statements shall be made by 9:00 p.m. (EST) that same day, and the parties shall meet and confer by 10:00 p.m. (EST) that same day to resolve such objections. Any disputes as to demonstrative exhibits shall be raised with the Court as appropriate before opening statements. The parties will not exchange closing demonstrative exhibits prior to closing statements (if allowed).

3. Demonstrative exhibits exchanged will not be used by the opposing party prior to being used by the disclosing party.

4. The parties agree that demonstrative exhibits that the parties intend to use at trial need not be included on their respective lists of trial exhibits. Plaintiffs' demonstrative exhibits will be identified with "PDX" numbers. Defendants' demonstrative exhibits will be identified with "DDX" numbers. The parties agree that copies of any demonstratives used during trial shall be submitted to the Court prior to the conclusion of trial in accordance with the Court's preferences.

5. The advance notification provisions for demonstratives intended for use in direct examination do not apply to demonstratives used during opening statements, to demonstratives used during closing arguments (if allowed), to demonstratives used during cross-examination, or to demonstratives created in the courtroom during live testimony, or to demonstratives that are simply blow-ups, highlighted versions of, or call-outs of other exhibits (including the addition of non-argumentative headings) disclosed pursuant to Section 20.a, *supra*.

6. The party seeking to use a demonstrative will provide a color representation of the demonstrative to the other side in PDF, PowerPoint, or some other commonly viewable format, according to the schedule above. However, for video or animations, the party seeking to use the demonstrative will provide it to the other side in video file, unless the video or animation is embedded within a PowerPoint presentation, in which case the party seeking to use the demonstrative will provide the specific slides of the presentation in native PowerPoint format containing such video or animation to the other side. For irregularly sized physical exhibits, the party seeking to use the demonstrative will provide a color representation as a PDF of 8.5 x. 11 inch copies of the exhibits.

7. For each demonstrative/summary exhibit that is based on a document or documents produced or exchanged in discovery in this case, a party will disclose to the opposing party, either (i) on the face of the demonstrative/summary exhibit or (ii) in a table or other writing provided at the time the demonstrative/summary exhibit is exchanged, all documents, data, or information that form the basis of the demonstrative/summary exhibit, to the extent that there are such documents, data, or information. Such information shall include the respective trial exhibit numbers, including page numbers.

c. Witnesses

1. The parties will each provide to each other's counsel of record via email a list of witnesses that it intends to call in Court, live, by 7:00 p.m. (EST) one (1) calendar day before the witness is expected to testify.

TAB 21

21. JURY TRIALS

Not applicable.

TAB 22

22. NON-JURY TRIALS

A. The following shall be submitted to the Court no later than ten (10) days prior to trial:

On October 25, 2019, each side shall submit to the Judge and opposing counsel a trial brief or memorandum in accordance with Local Civil Rule 7.2 with citation to authorities and arguments in support of its position on all disputed issues of law. In the event a brief shall not be filed, the delinquent party's complaint or defense shall be stricken.

B. The following shall be submitted to the Court after trial:

Following trial and on a date to be determined by the Court, each side shall submit to the Judge and opposing counsel post-trial proposed written findings of fact and conclusions of law.

Counsel shall provide the Court with a copy of its proposed findings of fact and conclusions of law on a computer disk in a WordPerfect readable format.

TAB 23

23. TRIAL COUNSEL (List the names of trial counsel for all parties).

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TAB 24

24. BIFURCATION

As there are currently no claims for damages from either party, there is no need for bifurcation of claims at this time.

TAB 25

25. ESTIMATED LENGTH OF TRIAL

The parties estimate 2 days for liability and 0 days for damages since the latter is not an issue. In accordance with the Court's August 19, 2019 text order, trial before Judge Chesler will begin on November 4, 2019 at 9:30 am (EST).

Dated: September 25, 2019

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Attorneys for Defendant
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Entry of the foregoing Joint Pretrial Order is hereby APPROVED this 2nd day of October, 2019.

Hon. Cathy L. Waldor
UNITED STATES MAGISTRATE JUDGE
United States District Court
For the District of New Jersey